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EDITORIAL RESPONSIBILITY IN RELATION TO HUMAN EXPERIMENTATION.[1]

By WILLIAM A. R. THOMSON, M.D.,
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Two major considerations weighed with me in accepting the invitation to participate in the discussion of this fascinating, if complex, subject. One was that as the editor of a medical journal I was directly implicated in the problem. The other was that all my own experimental work has been carried out on human beings or, in the crude scientific jargon of this year of grace, human guinea-pigs. I felt therefore that if as an editor I was critical of certain modern trends in human experimentation, I could speak, or write, with some first-hand knowledge of the problems which face those who carry out experiments on human beings.

Editorial responsibility in this matter takes two forms. In the first place there is the editor's responsibility for moulding medical opinion on the subject by the views which he expresses in his editorial comments. In the second place there is his responsibility for accepting or rejecting articles based upon human experimentation. Whilst all of us may be faced with this latter problem, and it is only some of us, probably the minority, who are faced with the former problem, it is perhaps this minority who can play the most important role in helping to maintain those standards of medical practice that are the *sine qua non* of an honourable profession.

[1] Read at a meeting of medical editors at the eighth General Assembly of the World Medical Association, Rome, September, 1954.

The Moral Code.

What are the fundamental facts upon which our views on this subject must be based? The first, and most obvious—and as good journalists you will forgive my carrying into practice one of the ten commandments of good journalism: never take the obvious for granted because it is the one thing your readers always overlook—is the moral code which we have all accepted as the basis of good practice. Personally, I prefer the phraseology of the old Hippocratic Oath:

> I will follow that system of regimen which, according to my ability and judgment, I consider for the benefit of my patients, and abstain from whatever is deleterious and mischievous. I will give no deadly medicine to anyone if asked, nor suggest any such counsel.

Perhaps, however, and especially before an audience meeting under the ægis of the World Medical Association, I should give priority to the modern version—the so-called Declaration of Geneva:

> The health of my patient will be my first consideration. I will maintain by all the means in my power, the honour and the noble traditions of the medical profession. I will maintain the utmost respect for human life, from the time of conception; even under threat, I will not use my medical knowledge contrary to the laws of humanity.

In other words, in no circumstances must we do anything to our patients that may cause them unnecessary pain or discomfort, not to mention any danger to life. They are human beings, with all the hopes and fears, ambitions and emotions, which we ourselves possess. They are not interesting "cases"; they are not ciphers to be

juggled with in the pursuit of knowledge; they are not pawns to be thrown on the chessboard of the statistician. The price of knowledge can be too high and we must ever ensure that it can never be said of the physician that "he that increaseth knowledge increaseth sorrow". The sheet-anchor of medical practice is the sanctity of human life. Once we let go of this, we are lost. To those who think that I exaggerate, or overstate the case, I would only say this: look at what happened in certain European countries during the 1939-1945 War.

"Integrity without knowledge is weak and useless", wrote Dr. Johnson, "and knowledge without integrity is dangerous and dreadful." That, I would suggest, epitomizes the whole problem. Provided we maintain our professional integrity in our pursuit of knowledge, we shall not submit our patients to procedures or treatment which might do them harm.

The Need for Human Experimentation.

The second fundamental fact upon which our views on this subject must be based is the necessity, sooner or later, for every new procedure or form of treatment being tried out on human beings. The problem here is "how soon?". So far as drugs are concerned, I am one of those who believe that this should take place as soon as possible, and even occasionally if the results of animal experiments are not too promising—provided always that we know the full toxicity of the drug and can therefore guarantee that it will do our patients no harm. Some of us were brought up on, and passed on in our turn, the somewhat cynical advice that the first criterion of a drug to be used in medicine was that it must do no harm. That may have over-stated the case, but it did bring home the fact that lack of toxicity was a prime consideration. If this criterion is satisfied, then a drug should be brought to the clinical trial stage as soon as possible. Although careful pharmacological and bacteriological investigation often tells us the full story of what a drug can do, or cannot do, there are instances in which a drug has proved much more beneficial in man than appeared possible from the results obtained in the laboratory, and much unnecessary time may thus be lost before patients can enjoy the benefit of the new remedy.

Animal experimentation we must always have, but I am one of those who believe that much more experimentation could usefully be done on patients, provided always that this does not expose the patient to any toxic hazard, does not delay his recovery, does not submit him to more than minor inconvenience or discomfort (such as, for example, venepuncture) and, above all, does not deprive him of the full or immediate use of what may be a life-saving procedure.

The Problem of the Controlled Clinical Trial.

This last point brings me to a relatively new problem which has been presented to us by the controlled clinical trial. Have we the right, as doctors, to deprive a patient of a life-saving drug in order to obtain sufficient "controls" to satisfy the statistician? I recall vividly the conference called at British Medical Association House in the early days of streptomycin to discuss the public outcry at the shortage of supplies and the pathetic appeals which the British Broadcasting Corporation insisted on sending out for supplies of streptomycin for children dying from tuberculous meningitis. At that time all available supplies of streptomycin were being controlled by the Ministry of Health and being issued only to approved centres for use in a controlled investigation of the antibiotic in tuberculous meningitis and certain prescribed forms of pulmonary tuberculosis. The official view advanced at the conference, of course, was that this was the best means of using the limited supplies available at that time in the United Kingdom, as it would ensure that in the shortest possible time we would know the precise value of streptomycin in a hitherto invariably fatal disease. I was sitting beside a distinguished medical editor whose small son was just recovering from a severe illness which at one time had been considered as possibly tuberculous meningitis. As the portentous, and scientifically sound, reasons were being repeated again and again in favour of the official policy, my neighbour turned to me and said that these arguments were all very well in theory, but, as a father, he had quite made up his mind that, by hook or by crook, his son was going to have every gramme of streptomycin he could find should the diagnosis of tuberculous meningitis be confirmed—controlled clinical trial or no clinical trial!

Who was right? The statistician and the clinical scientists looking at the problem with the cold objectivity of science and deciding that, in the long run, theirs was the way whereby the best use could be made of the available supplies, or the father determined at all costs that his child should receive the one drug that might save his life? I know not the answer, and I confess, quite unashamedly, that I am thankful that I have never been engaged in a clinical trial in which I had to agree to certain patients being deprived of their only hope of life. Is our criterion to be Francis Hutcheson's dictum, in his eighteenth century treatise on "Concerning Moral Good and Evil": "that action is best, which procures the greatest happiness for the greatest numbers"? As an editor, I say "yes". As the physician at the bedside, or as a parent, I doubt whether I would give much thought to the unknown "numbers". And would I be wrong if I thus heeded the Declaration of Geneva that "the health of my patient will be my first consideration"?

To revert for a moment to my contention that there was scope for more experimentation on patients, a point which should be made is that, subject to the provisions which I have mentioned, it is the patient's duty or, if you prefer it, privilege to make what contribution he can to the betterment of our means of preventing and curing disease. We do not hesitate to appeal to the public to bequeath their eyes to eye-banks in order that we may be able to use their corneæ to save the vision of patients who otherwise would be blind. Why should we not also assume that patients should play their part in relieving other inflictions of mankind?

Editorial Responsibility.

Finally, I come to the question of editorial responsibility for rejecting articles on the ground that they are based upon human experiments which are out with the accepted moral code for the profession. The answer, I would suggest, is that in such matters the editor must be guided by the same code as applies to every other member of the profession. If he conscientiously believes that the article submitted to him is based upon practices which have violated this code, then his duty is to reject it, even though by so doing he may lose the opportunity of publishing an epoch-making article. But in so acting he must be very careful indeed that he has taken all the relevant factors into consideration and that he is not depriving the profession of information of value, on inadequate grounds. Among the factors that would need to weigh with him would be the integrity of the contributor, the state of the patient and his (or her) reaction to the particular procedure involved. There can be no hard or fast rules in these matters. What is justified in the case of a patient who is suffering from a mortal disease, or who is in such excruciating pain that life is utterly intolerable, might well be wholly unethical in a patient suffering from a non-fatal condition or a condition in which the pain could be relieved by less drastic procedures. Again, a patient may have given his willing consent, even though he realized that the consequences might be detrimental or even fatal. "Safety first" is one of the most reprehensible slogans that was ever invented. Why should not a patient with some chronic condition, for instance, be allowed to submit himself to some new form of treatment, even if the consequences are not fully known? He may well have decided that the risk is worth taking, and if he takes it at the hand of a doctor, whether physician or surgeon, of integrity and skill, there is no good reason why he should not do so. At the selfish worst he is still a chronic invalid, but knowledge has been advanced. At the best he is restored to a fuller life, and all the other victims of the condition can look forward to benefiting from this first crucial experiment.

Conclusion.

I have been elementary—deliberately so, and I make no apology. In this mid-decade of the twentieth century we are all being so clever and advanced, and talking in such scientific jargon, that we are forgetting the moral code upon which all human conduct must be based if humanity is not to be lost in the maelstrom of atomic chaos into which modern science is threatening to throw us. So far as we doctors are concerned that moral code is epitomized in the Hippocratic Oath or, if you prefer it, the Declaration of Geneva. It is for the individual doctor, whether engaged in domiciliary, or in hospital, practice, whether at the bedside or in the laboratory, to determine his actions by that oath, always remembering, in the words of Tennyson, that "knowledge comes, but wisdom lingers". So far as we as editors are concerned, our duty is always to keep these tenets before our readers, and not to hesitate to criticize when criticism appears necessary. Our task would be much simplified if over the portal of every institute of clinical research there were carved these lines from Lord Tennyson's "In Memoriam":

> "Let knowledge grow from more to more
> But more of reverence in us dwell."

HEREDITY IN DISEASE.[1]

By HENRY RISCHBIETH,
Adelaide.

YOU may feel that the study of heredity — medical genetics — is a subject that does not affect you; you may consider that it is merely concerned with the collection of pedigrees of abstruse diseases, which feature in the text-books, but which you will seldom if ever meet in your practices. While this is a very widespread belief it is, of course, very far from the truth.

Before going further perhaps one might define disease as the result of disharmonious interaction betwixt constitution and environment. It should at once become obvious then that study of the constitution—in other words, genetics—may well be as important as the study of the environment.

At this I feel sure that most of you will metaphorically shrug your shoulders and say to yourselves fatalistically: "Oh yes, that is possibly true, but where does it get us? We can't alter our constitution." And that in our present status of knowledge is probably largely true; but every piece of information gleaned takes us another rung up the ladder of knowledge. At the same time we would do well to remember that much has already been achieved in regard to hereditary affections, and the prospect of the eventual control of the genetically determined conditions has become much less remote.

At the two extremes of this previously mentioned interplay between environment and constitution, either alone may produce disease, as, for example, in the injury produced by a burn or that produced by an inherited gene in, for example, gargoylism. How much more often, however, do other factors have to come into play also before disease is manifest, how often do we require both an environmental pathogen and a constitutional susceptibility, how often does the inherited characteristic show only in part, for example, in tuberculous infection, how seldom do we develop overt tuberculosis, or in Rh blood group incompatibility how seldom do we see erythroblastosis?

Since the dawn of medicine there has been an ever-changing emphasis, now on environment, now on constitution; during the past fifty years, in which science has made such progress, the major stress has been on environment, for during this period bacteriology, this term being used in its widest sense, has been very much in the van. Now a stage has been reached at which so many infections can be controlled that we must take stock of the position, and it will be readily appreciated that the starting point for further advance must be the constitutional factor.

What, then, is meant by constitution? One must confess that the definitions are rather nebulous—the habitus, formation or mould of a body, the inherited character of an individual. Perhaps we can do no better for our present purpose than to describe it as the inherent physiological and anatomical structure of an individual. But at once we will be in trouble, because constitution may have been moulded and influenced by such factors as maternal environment during development as well as the inherent genetic structure.

Medical genetics represents an attempt to clarify some aspects of the constitutional basis of disease.

In some affections only exhaustive investigation will reveal any hereditary factor, in others it is very plain; in yet others so far we cannot recognize the genetic factor, but perhaps this is a matter of not seeing the wood for the trees.

In 1865 the Abbé Gregor Mendel carried out the work with plants which provided the base on which all genetics stands. Ten years later chromosomes were discovered, and it was also demonstrated that at fertilization fusion took place between the nuclei of two sex cells. Ten years later again it was found that hereditary traits were localized in the nucleus of the cell and that the chromosomes split longitudinally and were reduced to half when the sex cells developed. Some fifty years ago there was a rediscovery of Mendel's work, and rapid progress followed; it was soon noticed that the distribution of chromosomes explained Mendelian splitting and that during sex cell formation the chromosomes were distributed independently of each other in conformity with Mendelian laws. It was soon found, however, that acquired properties were not inherited, but that at times mutation took place and a fresh inherited character appeared. Until forty years ago, when Morgan, following up Weismann's postulate that the chromosomes of the germ cells carried the hereditary material of the body, suggested that hypothetical genes were the actual bearers of the individual hereditary characteristics, little interest had been taken in genetics, and knowledge on the subject was very scanty; since then some of the shadows have lifted, and now where once was darkness there is some dawning of light.

Let us now consider something of the modes of human inheritance; some sixty years ago it was shown that during cell division the changes taking place in the nuclei of somatic cells were different from those observed in the germ cells, spermatozoa and ova.

As you know, human somatic cells contain 48 chromosomes, arranged in 24 pairs; when cell division takes place each of the 48 chromosomes splits longitudinally, and each daughter cell becomes a complete replica of the mother cell. In the division of germ cells there is dissociation of the pairs; not the individual chromosomes, but the pairs are split, so that a reduction division occurs to form daughter cells each containing 24 chromosomes. After fertilization, when the sperm carries into the ovum its 24 chromosomes, there is rearrangement to make in the fertilized ovum once again 24 homologous pairs, as in the somatic cells.

As mentioned before, division of vegetative cells takes place by mitosis. At rest the separate chromosomes are not visible but retain their individuality; then at the start of division they shorten and thicken, arrange themselves across a spindle, and finally split longitudinally and half of them go to each pole to form two daughter nuclei. In all divisions except maturation division of sex cells or meiosis, the chromosomes are arranged in homologous pairs, one from the female, one from the male—24 pairs in humans, similar in size, shape and structure.

In meiosis or sexual division there is halving of chromosomes—each gamete contains only one partner from each chromosome pair. During meiosis two divisions of the nucleus take place with only one division of the chromosomes.

[1] Read at a meeting of the South Australian Branch of the British Medical Association on June 17, 1954.

At the start of meiosis the chromosomes are seen as non-split, thin, beaded threads forming strings of chromomeres. The homologous chromosomes come together in pairs side by side (conjugation), and after pairing the chromosomes coil round one another and then split longitudinally into two chromatids; the four chromatids from a homologous chromosome pair remain closely associated for a period before they uncoil and fall apart in pairs, the pairs being held together by exchange of partners among the threads.

During pairing, crossing-over takes place in a way such that chromatids in homologous chromosomes break at identical points with exchange of chromatid segments containing one or more whole chromomeres.

After crossing-over has taken place, the split chromosomes (pairs of chromatids) move away from each other, tearing the chiasmata, shorten and group themselves inside the nuclear membrane; soon this membrane bursts and a spindle forms, shortly followed by the movement of the homologous chromosomes (pairs of chromatids) to each pole. Thanks to the crossing-over, the individual chromatids may contain both maternal and paternal material. Next follows division of the chromosome centromeres, hitherto undivided, and then finally segregation of the chromatids.

Thus four daughter cells, each with a halved chromosome number, have been formed. In the male all are equal; in the female, one is large, the ovum, and the other three are small polar bodies, which are discarded.

In fertilization the sperm with its war head of hyaluronidase torpedoes its way through the intercellular substance between the cells surrounding the ovum and penetrates the latter. After a short period of "standoffishness" the two nuclei soon fuse, and the zygote or fertilized ovum is formed with pairs of chromosomes once more, one of each pair coming from each parent.

Thus it can be seen that the hereditary influences of male and female are roughly equal. In all races of humans (as in monkeys and hedgehogs) there are 24 pairs of chromosomes; so each race may be crossed with any other—a practical experiment long since carried out. Chromosomes vary widely from cell to cell and from person to person, but they may often be seen to resemble beads (the chromomeres) on threads. The chromomeres occur in different sizes, arrangements and numbers which are characteristic of each chromosome of a species. It is believed that the chromomeres are the envelopes that contain the genes.

So far it has been suggested that there are 24 pairs of chromosomes alike in size and shape (but not in hereditary material)—these are allelomorphs; but in one sex (in the human, the male) this is not so in regard to one pair (the sex pair), which are not alike in size or shape, and these are called the autosomes. In one sex are found two different sex chromosomes, the X and Y chromosomes, the Y being much shorter. The other sex has two X chromosomes similar to the single X chromosome of the male. In the reduction division in the male equal numbers of gametes containing X and Y chromosomes are formed, but the female can produce only X chromosome gametes; so at fertilization equally often zygotes containing XX and XY chromosomes will be formed, the former being homozygous, the latter heterozygous; the former is a female, the latter a male. The genes, or hereditary factors which determine a character in the adult organism, act as units in the crossing over; during gamete formation the two partners of the gene pair separate and then recombine freely. During mitosis each gene divides into two identical with the original. On each chromosome the genes are linked in order, and unless crossing over takes place they go together to the same gamete.

The genes are able to continue identical reproduction by simple division, and although they show their effect on the organism as enzymes, they more resemble viruses and bacteria in their ability to multiply indefinitely in living tissues (although this reproduction depends on cell division) and in their ability too to undergo changes by mutation. The genes are probably of the size of medium-sized protein molecules and thus considerably smaller than many viruses; they are the basis of the synthetic chemical processes in the cells and thus in the whole organism; they control the processes of cellular metabolism and the synthesis of protein and other organic chemical compounds, which are conveyed from the nuclear system to the cytoplasm and so outward to react with environment. Biochemical genetics has shown that the actions of some genes are relatively simple, the ability to produce or not a single enzyme determining the absence or presence of a characteristic disturbance of metabolism, for example, in alcaptonuria.

The 48 human chromosomes have been estimated to carry between 10,000 and 80,000 pairs of genes of three types—major genes, polygenes and supergenes.

(*a*) Major genes are those in which differences or mutations are enough to be identified by their individual effects; these genes determine the development of the normal genotype, and most mutations of them are harmful, producing typical hereditary abnormalities or diseases.

(*b*) Polygenes are those in which mutations or differences are too slight to be identified by their individual effects; they often determine the development of predisposition to disease, for example, tuberculosis.

(*c*) Supergenes are groups of genes transmitted as single units or situated along a segment of chromosome; Rh, M-N-S and s blood group genes are considered to belong to this group, and their action is often due to chromosome rearrangements and abnormalities; supergene mutations may cause malformation syndromes, which of course may be caused also by a single major gene.

Each gene is to a certain extent independent, although each is dependent on the rest of the genotype; each is part of a family unit; genes on the same chromosomes are especially related both functionally and morphologically. For all that, each is mainly concerned with only one character, but it may also somewhat influence many others, and others may influence it. Whether a gene produces demonstrable effects depends on the strength of the gene in question, on the modification effected by other polygenic genes and on the environment in which it has to function.

It is also possible, although unproven except in plants, that cytoplasmic inheritance may occur.

Inherited disease is a condition which is determined wholly or in part by the hereditary constitution with which the organism started its development; this make-up, as we have indicated, consists of discrete and stable units (the genes), which are carried in the chromosomes in linear order like beads on a string. Every chromosome and every gene is present in duplicate in the body cells of the organism (except the sex chromosomes and the sex-linked genes)—one from the male and one from the female.

Now any disease which is gene-controlled has a causal genesis—the gene; but the actual mechanism by which this carries out its effect is known as the formal genesis. In many disease states there is a different emphasis on the two phases which go to produce it—the subject, and the specific environmental stress; both may vary. Just, for example, let us consider you—my audience. You are all in the same environment, you are all hearing me utter the same sounds, but the impact on you will be different; you will all put your own interpretation on what you hear; and so with disease—bacteria are not disease, they may produce it only by their reaction upon the individual in a certain environment.

At one end of the scale lies heredity and at the other environment, as exemplified by hæmophilia or a burn respectively; between lies most disease influenced by both. Just in passing one should point out the confusion between congenital and genetic disease. It is obvious that many conditions present at birth are not biologically inherited—for example, congenital syphilis and the cataracts or deafness after maternal rubella—while many inherited diseases show up only much later—for example, Huntington's

chorea, Friedreich's ataxia, some senile cataracts, the liability to coronary artery disease, rheumatic fever, and so on.

It should be remembered that our genes control our beginnings, our adult life and our senile degradation. In its first eight weeks the fœtus increases in weight 33,000 times per week, from the ninth to fortieth week by 90 times per week, after birth by one-fiftieth per week, and thereafter ever more slowly; so abnormalities are very noticeable if rate changes take place in the genetically determined growth potentials in fœtal life; in the abiotrophies they are less obvious.

Hereditary Transmission.

Abbé Mendel discovered the laws of transmission of individual genes when he carried out his classic experiments on garden peas; he observed that genes were transmitted independently and that any number of characters might be combined freely, each character being determined by a gene pair, of which one was derived from the father, the other from the mother. The two allelomorphs of a gene pair may be homozygous, if similar, or heterozygous if different; if they are heterozygous, one may be dominant and the other recessive.

Any disease due to a dominant gene will manifest itself if the gene is inherited from one parent only. As most inherited diseases are rare, the child will inherit it usually from only one parent and will transmit it to half his offspring; the disease, if the gene is fully dominant, never skips a generation.

In such a case the risks to the offspring can be simply calculated:

1. If neither parent has a given condition, neither will the child, no matter how many relatives show it.

2. If both parents have the disease, and if both are heterozygous, there is a 75% chance of the child's being affected ($Aa + Aa \rightarrow AA + 2Aa + aa$); if one is homozygous, the chance is 100% ($AA + Aa \rightarrow AA + Aa$).

3. If one parent has the disease and is homozygous, the chance is 100% ($AA + aa \rightarrow 2Aa$).

4. If one parent has the disease and is heterozygous, the chance is 50% ($Aa + aa \rightarrow Aa + aa$).

If the disease is due to a recessive gene, it will show out only if the gene in question is received from both parents; that is, it shows in 25% of the offspring of unaffected carriers, while 50% of the offspring become carriers and 25% are quite free of the trait. It will be seen that recessive diseases are therefore widely scattered and may at first sight appear spasmodic; they often skip generations and show up most where inbreeding has taken place. They may be transmitted unsuspected through many generations. With recessive disease the risks to the offspring can again be calculated:

1. If both parents have the disease (a rare happening), 100% of children will be affected ($aa + aa \rightarrow 2aa$).

2. If one parent shows the condition and the other is a carrier, 50% of children will be affected and 50% will be carriers ($aa + aA \rightarrow aa + aA$).

3. If one parent shows the condition and the other is normal, 100% of children will be carriers ($aa + AA \rightarrow 2aA$).

4. If both parents are carriers (one of the grandparents on each side has had the disease or a previous child has shown the condition), 25% of the children will be affected and 50% will be carriers ($aA + aA \rightarrow aa + 2aA + AA$).

5. If there is one carrier in each of the maternal and paternal groups, 6·25% of children will be affected and 37·5% will be carriers.

Sex-linked inheritance in humans occurs with certainty only with X-linked characters. X-linked recessives appear in the male as dominants, but in the female only when the gene is found in both X chromosomes; they are transmitted through unaffected females to affected males, being passed from generation to generation through an affected male's unaffected but carrier daughters or through an affected male's unaffected sisters, 50% of whom are carriers—for example, in hæmophilia. Similarly red-green colour blindness is often a sex-linked recessive, present in about 5% to 7% of males and 0·25% to 0·5% of females, but in addition some carrier females show poor colour aptitude.

In man there is good evidence that linkage occurs between some pairs of traits, but in most the evidence is unsatisfactory; it appears probable that the genes for red hair and ABO blood grouping are linked, and in the X chromosomes the genes for hæmophilia and partial colour blindness have been shown to be linked, and crossing-over may take place.

Severe hereditary diseases or inherited defects are as a rule the result of major gene inheritance; but in man I think it is probable that far more important really are the polygenes, which cause continuous variations in characters and often determine the development of predispositions to disease; in this case several pairs of genes produce more or less cumulative effects on a character.

The supposedly normal characters in man—build, height, intellect, stamina *et cetera*—are examples of the effect of a number of genes, and it seems probable that characters such as resistance to tuberculosis are similarly the summation of the gene effects.

At times lethal genes are found; naturally enough, in the living organism they can exist only as heterozygous recessive characters. These lethal genes may exert their effect at any stage of development. In humans, amongst whom inbreeding of the type carried out by stud breeders does not occur, the lethal and sublethal genes are of less importance. As well, however, as lethal and sublethal genes there are undoubtedly other genes which influence viability and vitality, and which lead to longevity or the converse; these are likely to be of the nature of polygenes, each affecting such characters as liability to malignant disease, resistance to infection and so on, all together leading to a genotype who may, barring accidents, live to old age.

As well as characters which are inherited unchanged from generation to generation there occur every now and then sudden persisting changes of heredity; these are due to mutation or changes in one or more genes. Such mutation may occur spontaneously or as the result of noxious trauma to the genes. The spontaneous mutation frequencies known in man are of the order of from 1:10,000 to 1:100,000; that is, mutation occurs in one out of 10,000 to 100,000 gametes. Individual gene mutations are as a rule recessive, mutations of structure (changes in the number or succession of genes) are apt to be dominant; many mutations, however, are probably intermediate. It is believed that favourable intermediate mutations gradually become dominant, unfavourable ones recessive; evolution tends to establish dominance of the normal in relation to the pathological, which renders the individual less viable.

It appears likely, as was first suggested by Apert (1907), that hereditary diseases in man not infrequently arise through mutation; this applies largely to recessive diseases, but may occur also in dominant lesions, as has been shown to occur in Huntington's chorea.

Any disease which depended entirely on hereditary factors would over a number of generations breed itself out because of the reduction of fertility of the individuals suffering from it; to keep the disease occurring at an approximately constant rate through successive generations requires a mutation rate approximately equal to the loss as a result of impaired reproductive fitness.

In any hereditary disease a certain number of affected persons dies early and therefore does not reproduce; sterility and reduced numbers of children lead to a steadily decreasing frequency of the pathogenic gene. For example, if the reproductive fitness was three-quarters of normal, then in five generations the gene frequency would be reduced to $(\frac{3}{4})^5$ or less than 25% of the original. If the rate in the community remains constant then mutation must be occurring at an equal rate. Calculations can be

made which for some diseases give a rough approximation of the mutation rate; this has been done for hæmophilia, which it has been calculated must have affected every man in England in 1066 if no mutation had occurred since. It has been estimated that the mutation rate for this condition is approximately 1:20,000 per chromosome per generation; this may occur in any of the three X chromosomes (two female, one male) involved in each generation. This rate is probably higher than for most genes.

As well as these spontaneous mutations there may occur mutations artificially produced, as by X rays, radium, atom bombs *et cetera*. If a dominant mutation is produced, it will be manifest in the offspring. Similarly generally a sex-linked mutation will show in the first or second generation, but a recessive mutation will show not sooner than the third generation and then only under genetically favourable conditions; so that we should in our wills perhaps leave an instruction to our grandchildren or great-grandchildren to avoid the grandchildren or great-grandchildren of radiologists and atomic scientists. However, it should be borne in mind that it has been estimated that while spontaneous mutation produces abnormalities in one or two per 1000 births, a dose of 800*r* increases the risk of an hereditary defect only to 1%, 99% of the children will remain normal, so perhaps we need not worry.

Intermarriage in general probably involves little or no risk in thoroughly normal families; it does not create weaknesses or defects, it merely brings them to light. It is a fortunate family which can be sure that there is no skeleton in the cupboard in the shape of recessive disease which may be transmitted through several generations without discovery. With rare recessive disease consanguineous marriage in the parents is common; where the recessive disease is more common, intermarriage is less pronounced.

Not all such consanguinity is bad; for example, the Darwin family were the offspring of cousins. Likelihood of Rh incompatibility between mother and fœtus is smaller in consanguineous matings.

Now it has been shown that one in 80 births is a twin birth, one in 80^2 a triplet birth, and one in 80^3 a quadruplet birth. Of all twins 25% are identical. Two-egg (fraternal) twinning is often an inherited characteristic, but one-egg twinning is probably not; two-egg twinning also increases with maternal age up to the middle thirties. Identical (one-egg) twins are on the whole less strongly developed than fraternal twins and are very often premature; often, although genetically they are identical, there may be quite marked differences, physical and mental, as a result of their different maternal environment.

Mirror imaging of greater or less degree occurs in almost 50% of all identical twins; in fraternal twins it is much less common, although here left-handedness is twice as common as in the population at large.

Hereditary disease in some cases can be traced through many generations—for example, Hapsburg lip, Shrewsbury hand, Huntington's chorea. Most family trees allow only a few generations to be fully plotted, but this is sufficient as a rule to allow identification of the genetic nature of the disease and assessment of the probabilities for future members of the family.

In most hereditary diseases there is a negative selection because of the lower reproductive fitness of people suffering from these conditions. Total negative selection means that the person with the character is entirely prevented from propagation. This in dominants stops the line immediately; in recessives, if common, it reduces the incidence rapidly, but, if rare, it is much less effective.

This has assumed that mating in the population is random, but it is not. Assortive mating of greater or less degree is common; people of similar intelligence or build or artistic ability *et cetera* are likely to marry, while two redheads or two quarrelsome people are not. These considerations are likely to upset calculations.

Whether any disease is hereditary can often be determined very rapidly. If there is no skipping from generation to generation and one-half the offspring of affected individuals show the condition, then the condition is likely to be a dominant. If there is scattered occurrence in the family and approximately one-quarter of the siblings of the affected individual are themselves affected, a recessive condition is probable. If the disease occurs in males and is inherited through unaffected daughters of affected males, then it is a sex-linked recessive, and so on. Many family trees, however, because of small families, do not allow such a decision to be made.

Studies of a condition must then be carried out statistically by collecting details about the parents and siblings of many affected individuals, care being taken that accurate information is obtained about all healthy as well as affected members of the group; if information is available about the propositus, his offspring and his nephews and nieces, his grandparents and his parents' siblings, and possibly their offspring, a much better picture may be obtained.

Care must be taken that the series is not a biased one by selection of the original group but is representative of all patients with the disease.

The figures are then analysed by several methods, the simplest of which is the sib method. In this affected and unaffected siblings of the propositus are counted, the affected individual himself being excluded; each sibship is counted as many times as there are affected siblings. If there is no selection, the ratio for dominant disease should be 1:1, and for recessive disease 1:3; in practice, figures of 30% to 40% and 15% to 20% are more usual. At the same time, control series from the general population must be compared. Studies of one-egg and two-egg twins will give further useful information about hereditary disease because of the high concordance in identical twins and a less or absent concordance in fraternal twins; while if it is not hereditary, discordance is just as frequent in uniovular as in di-ovular twins.

Normal development is probably largely genetically determined. We know that such characters as dwarfing are passed by pathogenic genes; so that there must be normal allelomorphs which ordinarily control rate and extent of growth. We know, too, that there are sex-linked genes for baldness; so that there must be genes for hair growth, and so through the whole gamut of development. Hair colour (if we have any) is genetically determined; dark hair is usually dominant to blonde, while redheads owe their glory to a special gene. Eye colour, too, depends on a number of genes, blue eyes being usually recessive to brown, although sometimes even in the absence of the milkman two blue-eyed people produce a brown-eyed child.

Our fingerprints, which may be a subject of importance or embarrassment to some of us, again depend to a large extent on hereditary factors; although no two are identical, the arrangement of arches, loops and whorls follows a familial trend.

The development of our facial contours is largely genetically determined. I have for instance in my practice a child with bat-ears, whose father and grandmother at least show the same character to an extreme degree (both had the nick-name "Jumbo"), and it is not unusual to see siblings thus affected. Teeth, too, both in development and proneness to decay, show a strong hereditary influence. There is no doubt, however, that the human hereditary trait about which we know most is that of the blood groups, each blood group character being dependent on a single gene pair and most being inherited independently of any other. This allows the plotting of a number of chromosome pairs. The A B O groups of Landsteiner depend on three allelomorphs, A, B and O, allowing the formation of the four groups AB, A, B and O (the subgroups of A allow the division into a much larger number of groups). The remainder of the blood group systems, save one, seem rather academic, but this one has great practical importance as well as theoretical interest; it is, of course, the Rhesus blood group system. As you well know, in most white communities some 85% of people are Rh-positive and 15% Rh-negative; so that by random selection approximately one marriage in eight or nine will be between an Rh-positive father and an Rh-negative mother. In practice, only one baby out of every 200 or

300 or 400 does in fact suffer from erythroblastosis; so that other factors as well as *Rh incompatibility must be* involved.

The *desirability of Rh testing* of all pregnant women and determination of anti-Rh titre in Rh-negative women whose husbands are Rh-positive seems worthy of comment.

The subdivision of the Rh group with regard to CDE gene pairs requires no further mention at this stage, but I would again stress the *importance of* ABO and Rh grouping before transfusion if circumstances allow.

Blood group determination may be of importance medico-legally, in regard to determination of parentage and also in criminal law, but so far no other convincing evidence of relation of disease to blood group has been elicited.

Intelligence is largely hereditary. Upbringing and education may be *determinants of the degree* to which this character is developed, but they act merely as stimulants to or inhibitors of the hereditary factors which determine basic innate intelligence. Education and *other forms of* training influence concentration of will and thus may allow *improved performance*, but they affect intelligence but little. One will immediately think of some genius who has a child of very ordinary intelligence or vice versa; it is not genius that is hereditary but the mental elements which in fortunate combination may produce it. It is a depressing thought that it has been estimated that only one person out of 4000 should be classed as highly intelligent. I feel that that does not, of course, apply to present company or to other selected groups.

Some families seem to have a peculiar bent for a particular form of intelligence, being otherwise little removed from the rest of us; be it music, art, mathematics or even medicine. Or do exogenous factors play the major part here? Perhaps we should ask our President, or one or two members of the audience who come from "medical families".

Constitution is a term which comes in for a good deal of abuse because of the different meanings which are attached to it by different workers; some regard it simply as the genotype of the individual, while others regard it as the phenotype—in other words, the resultant of both heredity and environment. Depending upon which of these definitions we prefer, we will build our concept of allergic constitution and such like; it is not in this case heredity alone but more the genetically determined reaction to a peculiar set of environmental circumstances with which we are concerned.

That many diseases are of hereditary origin is apparent to us all, but it is perhaps less well realized that no less than 2% or 3% of the population suffer from severe hereditary affections and that more than 500 hereditary diseases are now known to exist in man. However, more important by far are familial "predispositions". All of you know families that always seem to be in strife; their resistance to infection is low, or they are apt to react to noxious stimuli in an unfavourable manner. Similarly one can think of other families in one's practice who are just as keen to call the doctor when ill befalls them, but whom one may see but once or twice a year; this, I feel sure, is a result of a tougher genetic makeup.

We will now go on to a brief consideration of some of the hereditary conditions which may be encountered in practice, and I will confine myself to diseases which have come within my own experience.

First, however, one should point out that some of these diseases manifest themselves at or very shortly after birth, while others produce symptoms and signs only at a much later stage of life, and here the hereditary nature may be much less obvious on superficial examination. As you will appreciate, many of the hereditary diseases are not very amenable to treatment. Or should one say that after treatment there is seldom restoration to complete normality? Treatment is often a two-edged weapon—if successful it frequently leads to an increased incidence of the disease.

Taking first things first we should consider the congenital physical malformations. Serious physical malformations occur in at least 1% of all infants, but many of these die, and so the defects are less frequent in the general population. *A number of them, too, are due* probably to maternal environmental conditions, such as *rubella and so on; but* we are left with many which are truly hereditary, being transmitted either as *dominants or* as recessives with variable rates of manifestation.

The development of the head and face *allows room for* many abnormalities, of which many are genetically *determined. Some cases of hydrocephalus* are hereditary; I have seen two cases in siblings who had also an uncle affected. Cranio-cleido-dysostosis (I have recently seen a family in which the father and *two children were affected*) is usually inherited as a dominant. In two other cases a *parent was also affected.*

In Crouzon's disease (cranio-facial dysostosis) with its parrot-like face, dominant transmission is usual; in the one family I have seen, grandmother and *one aunt were* said to be affected in addition to the mother and her only *child.*

Micrognathia is frequently a dominant anomaly.

Harelip and cleft palate are *amongst* the most common congenital malformations, occurring in approximately one *in 600* live births; a considerable number of those affected die, especially as some 10% have other severe *associated* malformations. Much confusion has, however, occurred because of the *failure to differentiate* between (i) harelip with or without cleft palate and (ii) isolated cleft palate, which are two separate malformations with quite different genetic behaviour.

Cleft lip *plus* palate is generally, if not always, a hereditary condition, transmitted often as a conditioned dominant with partial sex limitation to males and less manifestation of the heterozygous than the homozygous form; so that in some families the condition seems fully dominant, but more often it appears to be of recessive nature. In affected families absent or defective upper lateral incisors are common.

Isolated cleft palate is in many families, as far as can be determined, non-hereditary, but in others there is strong evidence of irregular dominance with partial sex limitation to females.

A person with harelip may safely marry a person with isolated cleft palate, but it would be unwise for either to undertake a consanguineous marriage or one with a person who has a similar defect in his family (unless it appears certain that it is an isolated cleft palate, and even this may represent a mutation).

Plagiocephaly or asymmetry of the skull is not infrequently of hereditary origin, being seen sometimes in siblings and their cousins. *Pectus excavatum* is seen as a dominant in some families, although some members may be only mildly affected.

Spina bifida is probably often of recessive origin. If advice is sought with regard to future children, the problem may be a difficult one. It is stated that the risk is of the order of 5%, but it is, of course, influenced by whether the parents have *spina bifida occulta* and whether the condition occurs in relatives.

I have recently met with a case in a second affected child in which a cousin of the father and a sibling of the mother showed *spina bifida aperta*; the condition is more frequent in females, and families affected not infrequently show other developmental abnormalities.

Congenital dislocation of the hip is commonly a familial disease, being frequently transmitted as a dominant with some sex limitation to the female (female : male = 6 : 1). There has been some argument about the gene(s) involved in this condition, because we find among the relatives of those affected frequent cases of partial dislocation or radiological flattening of the acetabulum; if this is caused by the same gene as complete dislocation, then the condition is a dominant, and some 10% to 15% of the offspring of an affected person will show the condition and some 35% to 40% more have minor evidence. In one family this condition has been seen in five generations; but as not all

were radiologically examined, the picture resembles more that of an irregular dominant.

Perthes's disease is not uncommon in the same families. It is seen in some families as a dominant, as in a family where the patient's father had been treated by my father and the grandfather "had had a bad hip since a boy". In others it appears to be recessive. In yet others it is probably sporadic and perhaps the result of mutation.

In syndactyly some families show a well-marked dominance, in others an incomplete dominance—as in a family of which I have a record and in which four generations are involved. In still others the condition, while possibly recessive, may be due to maternal environmental factors.

Talipes equinovarus is one of the common congenital abnormalities occurring approximately once in every thousand births and is probably hereditary in the vast majority of cases, as in one case in six a familial incidence can be demonstrated, and in one case in thirty a sibling is also affected. When homozygous the gene is likely to manifest itself only in some 25% of cases. In an occasional family full dominance appears to exist; more often perhaps the condition is recessive.

In the severe form of talipes associated with arthrogryphosis dominant inheritance seems to occur. In all families of talipes sufferers consanguineous marriage is unwise. Dupuytren's contracture is frequently an hereditary affection, but one which shows up only after middle life; often a dominant, it frequently shows a sex manifestation only in males, the females being but carriers.

Chondrodystrophy is a dominant condition occurring largely as a result of a fairly high rate of mutation, because chondrodystrophics have a high infant mortality and a greatly diminished reproductive fitness.

Arachnodactyly with its associated eye and heart defects is usually inherited as a dominant, although some members of the family may manifest only a partial syndrome; in the family of one affected person one uncle is six feet seven inches in height, but shows no other evidence of the condition.

Fragilitas ossium varies very much in its severity, but it is inherited in milder or more severe form as a dominant. In some cases the affected person shows only blue sclerotics, in others this *plus* deafness; in severe cases such severe fractures may occur *in utero* that survival of the infant is unlikely. It is worth mentioning that in two of my cases the affected persons have had in addition diabetes.

Gargoylism or Hurler's lipochondrodystrophy is regarded as a probably recessive disorder. In England I saw three siblings affected but without any other family history of the condition, and the two cases at the Adelaide Children's Hospital have been isolated ones.

Morquio's disease is generally a clearly marked recessive condition involving one gene. In the one case met with recently no family history of the condition could be elicited, and it may have occurred as a result of mutation.

Umbilical hernia may show a well-marked dominance. I recently saw a baby whose mother, grandmother and great-grandmother had large herniæ.

Hæmophilia is, of course, well known to you all as the classical example of a sex-linked recessive condition. In the family history of one of my patients five generations and 22 individuals are known to have been affected, although in the direct line it had been carried through the maternal side for four generations, and the mother did not know of its existence in the family till the patient first bled. It is perhaps worthy of comment that in this condition there is often one time of the year when these individuals are most prone to bleed; in the case in question the boy has had a bleeding episode requiring hospitalization over each of his birthdays save one and then two weeks later, and on only two other occasions.

Cooley's anæmia (Mediterranean anæmia), a condition of which we may see an increasing amount as the result of immigration, is inherited as a Mendelian recessive. The heterozygotes show a moderate hypochromic microcytic anæmia, splenomegaly *et cetera*; the homozygous condition is fatal in infancy or childhood.

Familial acholuric jaundice is inherited as a dominant, but it seems likely that mutation is not rare; the severity varies in different members of the same family and between different families, but spherocytosis and increased fragility are usual.

Pernicious anæmia is frequently an hereditary condition; some 30% of sufferers have another affected relative, and some 50% of their near relatives suffer from achlorhydria. It is a little uncertain whether it is the pernicious anæmia itself or the achlorhydria which is inherited.

Erythroblastosis is, of course, a genetically determined disease in so far as one's Rh status is an hereditarily determined character, but more than that one finds that only certain families who have the appropriate Rh set-up do in fact have affected babies. In a small series I have six mothers who have had a sister who has also had one or more affected babies; furthermore, in two other cases the father's sister has had an affected infant.

It seems likely that a-γ-globulinæmia, which is at present arousing interest because of its obvious relationship to poor resistance, is probably inherited as a dominant.

A number of the vascular diseases appear to have an hereditary basis, but it would require statistical investigation of many cases to be certain. It is common knowledge that in many families one finds a high incidence of hypertension, cerebral apoplexy, nephrosclerosis and heart disease. In one family three brothers died of hypertension and one of coronary occlusion below the age of forty years. Coronary artery disease appears often familial, as does cerebral hæmorrhage at a relatively early age, and it would seem that arteriosclerosis is a dominant disease.

Berry aneurysms are not infrequently familial.

Patent *ductus arteriosus* may occur among siblings and is at times possibly inherited as a recessive character. I have seen this condition in a mother and two siblings, and it is possible that with increased survival of those suffering from congenital heart disease other congenital heart disease will also be found to be of genetic origin.

However, it seems to me that in the abiotrophies we will find that heredity plays a larger part than we had so far appreciated—that many of us "wear out" before our time and that this is associated with our genetic makeup as much as with the environment in which we live.

Our resistance to infections as well as that to ordinary wear and tear is something for which we must thank our forebears, for I feel sure that these are the resultant of the effects of many genes.

Hypospadias, especially of the glandular type, is commonly inherited as a dominant, in one case for four generations; it is, of course, sex limited. It is of interest that one of my patients' mother's affected uncles was the father of 13 children.

Bronchiectasis appears in a certain percentage of cases at least to be inherited as a dominant characteristic; the severity and often the site of involvement are relatively constant among different members of the family.

Fibrocystic disease of the pancreas is commonly inherited as a recessive condition; the manifestation of the disease amongst siblings is rather constant—for example, meconium ileus, paroxysmal cough at the age of six months, and so on.

Hirschsprung's disease is irregularly dominant with some sex limitation to the male, but mutation is probably not rare. In one case two known fatal cases had occurred in earlier generations.

There is strong evidence that many cases of *diabetes mellitus* are hereditary, but whether one or more genes is involved is uncertain. The evidence in favour of juvenile diabetes being a recessive character is quite good, a high morbid risk for diabetes being present among siblings and offspring.

Glomerulonephritis sometimes seems to be a condition with irregular dominant inheritance; at other times no such familial trait is seen. Polycystic kidneys are often a familial condition.

Rheumatic fever or rather the predisposition to rheumatic fever is inherited as a recessive character in many cases, but environmental causes are the precipitating factor for an attack; some 30% of affected patients have an affected near relative.

Thyroid disease is another condition in which predisposition appears to be inherited, although it may occur only in the face of precipitating causes; it is considerably more common to find further cases among relations than among the population at large. Thyrotoxicosis is largely inherited as a recessive condition with sex limitation to the female. Asthma, hay fever and infantile eczema form a triad of allergic diseases, the predisposition to which is inherited as an irregularly dominant gene; but here again, as in so many conditions, environment plays its part also. Sometimes within the family the same forms of allergy occur; at other times it seems to be only the allergic tendency which is inherited.

Tuberculosis is a very widespread disease, the resistance to which is largely determined by environmental conditions; but hereditary factors play their part, too, and it is worth citing the case in which father and two children all died of tuberculous meningitis at intervals of a couple of years.

Poliomyelitis likewise shows not infrequently several cases in the family at quite different times. I firmly believe that whether paralysis occurs or not depends upon your heredity and that there is a great deal of information to be gleaned from the study of the family history of sufferers—but that is a story beyond the scope of these remarks.

Suffice it to say that I am at present carrying out a family history survey of persons suffering from poliomyelitis, and although I have at present no final figures, I pulled out several diseases this afternoon from the first hundred cards. They may not be a fair simple, but in these leuchæmia occurred three times in the grandparents' generation, twice in the parents', once among siblings and twice in first cousins. Rheumatoid arthritis occurred 38 times in grandparents, 21 times in parents, and twice in siblings. Diabetes occurred 35 times in grandparents, 21 times in parents, and twice in siblings. Poliomyelitis occurred four times in grandparents, 10 times in parents, and 10 times in siblings.

Without statistical analysis these figures appear to be more than twice and up to six times as high as the figures in 300 controls.

The position is similar with certain other diseases, such as coronary occlusion at an early age, asthma and several others which seem to me to be related.

It is worth mentioning that asthma, leuchæmia, diabetes, rheumatoid arthritis, chilblains, coronary disease and poliomyelitis are either unknown or very uncommon amongst aborigines.

Epilepsy is in some cases obviously hereditary, but the exact mode of inheritance is far from clear; probably polygenic factors are involved.

Friedreich's ataxia is another hereditary nervous condition in which the mode of transmission may be recessive or irregularly dominant. A decision may be made more difficult because some affected individuals show only very few stigmata.

In the skin there are many hereditary conditions. It will perhaps suffice to mention two or three. Ichthyosis may be transmitted as a dominant or a sex-linked recessive. Baldness (calvities) is frequently a dominant anomaly with sex limitation to men. In a case of congenital ectodermal dysplasia of the anidrotic type I was able to obtain a very extensive family history suggesting probably a sex-linked recessive inheritance, although it may have represented incomplete dominance with partial sex limitation to the male.

In the field of the ear, nose and throat surgeon some families appear to develop tonsils of poor quality. Others suffer from very frequent middle-ear infections through a number of generations; this I should like to postulate may be associated with direction of the Eustachian canal allowing greater or less stasis especially in the recumbent infant.

In the eye, where defects are perhaps more obvious than elsewhere, a large number of hereditary conditions have been observed. I do not propose to mention more than a few of the more common conditions.

Myopia and hypermetropia are probably the resultant of interaction of many genes, and it is only in an occasional family that clear evidence of the mode of inheritance is obtained.

Primary squint is inherited as a dominant in a large number of cases.

Cataract formation is in many families an inherited condition; but as it is a condition occurring late in life, this genetic relationship is much less apparent than in those conditions which manifest themselves early in life. It is, however, just as real. And so one might go on. I have but touched the fringe of the subject, but I hope that I may have aroused your interest in some of the aspects of heredity in disease.

In conclusion, I should like to read you an extract from another paper on this same subject.

> Mr. President and Gentlemen: I fear I do not much mistake in the belief that the subjects which I have ventured to take for my present course of lectures are by no means high in professional favour. Our forefathers, who knew far less about the details of pathology than we do, attached far more importance to such matters as temperament and diathesis. They were accustomed to prescribe for a man's temperament; we think only of his disease, and turn aside with weariness from the classifications of diathesis in which the physicians of an older day delighted. Although to a large extent this change of sentiment has been the result of advance in knowledge, yet I think it might easily be shown that it has gone too far, and that we now neglect unwisely the study of those differences between man and man of which, for the most part, physiology takes no cognizance, but which may yet prove of much importance in modifying the processes of disease. It is to this study that I now invite your attention.

The date was 1881, the lecturer Jonathan Hutchinson.

THE SURGICAL APPROACH TO THE FEMORAL CANAL.

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MANY of the difficulties experienced by a surgeon during the performance of any particular operation have as their basis inadequate exposure of the area concerned. Particularly does this statement apply to the region of the femoral canal. Whilst the generally practised methods of approach are adequate if the object is to close the femoral canal, they can lead to difficulties should any more complex procedure, such as resection and anastomosis of the small bowel, be found necessary. Often under such circumstances the abdomen is opened by a second paramedian incision in order to enable the resection to be performed. The approach described in the present paper is not subject to these difficulties, and, since it is not widely practised, it would appear reasonable to discuss it further.

Historical Survey.

The earliest attempts at repair of a femoral hernia were undoubtedly made via an approach through a skin incision under Poupart's ligament. It is difficult to trace the origin of this operation, but it is certain that the lower approach was well established before the middle of the nineteenth century. The ease and simplicity of this operation in suitable cases are obvious to all who have used the method;

however, the approach is possessed of the following disadvantages: (*a*) It is not possible to secure the neck of the sac flush with the peritoneum. (*b*) Should the hernia involve the bladder, that viscus may be damaged, in which case adequate reparative steps are impossible through this incision. (*c*) Should the femoral hernia be strangulated, it is obvious that bowel resection is impossible via the lower route. Moreover, the uncommon anomalous obturator artery—related to Gimbernat's ligament—is in danger during the manœuvres necessary to liberate a strangulated femoral hernia.

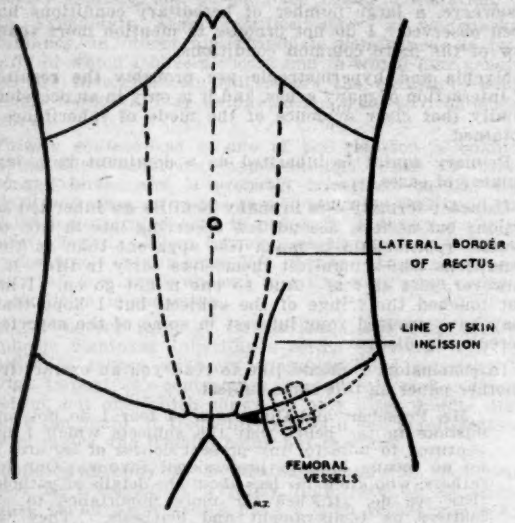

FIGURE I.

Diagram of the anterior abdominal wall indicating the position and extent of the skin incision used in this approach to the femoral canal. Its relations to the lateral border of the *rectus abdominis* muscle and to the femoral vessels are to be noted.

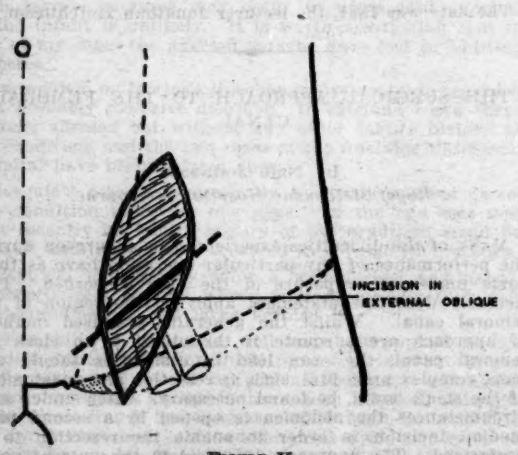

FIGURE II.

Diagram of the lower part of the anterior abdominal wall, showing the exposed aponeurosis of the external oblique muscle and the extent of the fibre-splitting incision in that muscle. Note that the fibres of the external oblique are split beyond the limits of the skin incision.

In view of these and other disadvantages, it is not surprising that attempts were made to cure femoral hernia by approaching the canal from the inner aspect. Annandale (1875) was the first surgeon to use the inguinal route of approach; Tuffier, writing in 1894, also advocated this method of exposure. However, it was not until the early part of the twentieth century that the approach became widely used. The writings of Lotheissen (1898) played a major part in the popularization of this operation, and he is often erroneously given the credit for originating the approach.

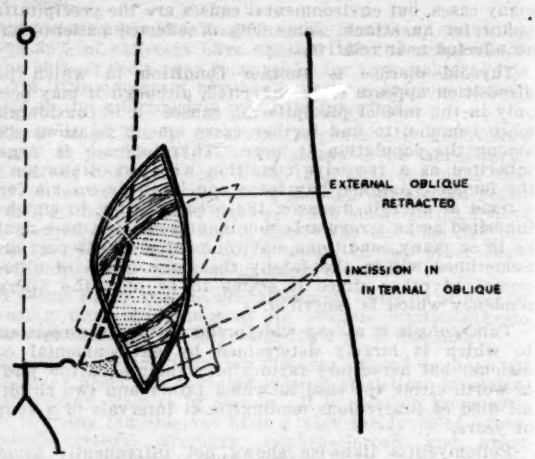

FIGURE III.

Diagram showing the lower part of the anterior abdominal wall with skin, subcutaneous tissue and external oblique aponeurosis retracted. The fibres of the combined aponeuroses of internal oblique and transversalis are revealed, and the line of incision through these fibres at the lateral edge of the rectus is to be observed.

Cheatle (1921 and 1922) was the first to devise an extraperitoneal approach to the inguinal and femoral canals. He used a transverse suprapubic incision, dividing skin and rectus sheath, and, after displacing the recti away from the mid-line, approached the femoral canal via the extraperitoneal route. Henry (1936) also used the extraperitoneal route, gaining access to the extraperitoneal

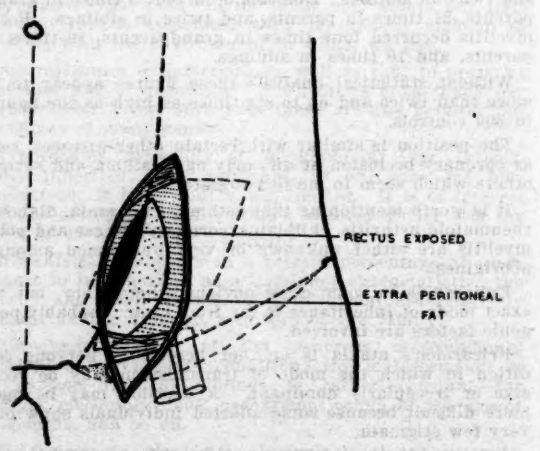

FIGURE IV.

Diagram showing the lower part of the anterior abdominal wall with skin, subcutaneous tissue, external oblique and the combined aponeuroses of internal oblique and transversalis retracted. The lateral edge of the rectus muscle and the extraperitoneal tissue are exposed.

plane by mid-line subumbilical incision. Whilst these methods of approach are useful when one is dealing with bilateral herniæ, they do not give direct access to the femoral canal and have therefore not gained great popularity.

The approach described in this communication has been described previously by McEvedy (1950), who makes no claim of originality for the method. However, its virtues are such that it should be more widely known.

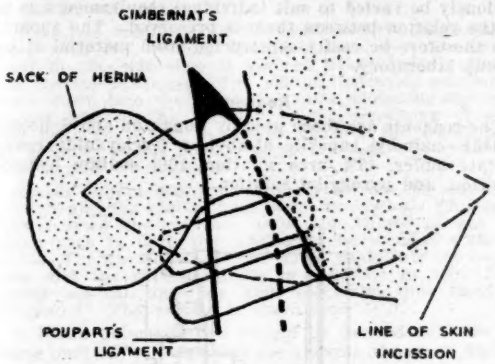

FIGURE V.

Diagrammatic representation of the exposure of the femoral hernia and canal as seen in the present operation. The line of the retracted skin incision is also indicated. It is clear that adequate access is gained to the three points of importance in this operation—that is, the hernial sac, the hernial canal and, if necessary, the peritoneal cavity.

Method.

A curved incision dividing skin and superficial fascia is made along the lower quarter of the lateral border of the rectus sheath, as shown in Figure I. Its lower end curves away from the contour of the rectus muscle so that it crosses the region of the femoral sac, the reason for this being that the sac and its contents are readily exposed through this part of the incision, should that prove necessary. A little dissection with undermining of the skin flaps will expose the external oblique aponeurosis, which is split along the line of its fibres as shown in Figure II.

Retraction of the external oblique aponeurosis will reveal the fused aponeuroses of the internal oblique and transversalis muscles (Figure III). Through the fibres of this aponeurosis one can identify the lateral border of the *rectus abdominis*. An incision, cutting across these fibres, is made along the line of the lateral border of the rectus muscle, the lateral border of the rectus and the *fascia transversalis* covering the extraperitoneal tissues (Figure IV) thus being exposed.

At this stage it is found that there is a constant, small neuro-vascular bundle running in the loose connective tissue between the combined aponeuroses and the *fascia transversalis*. This bundle is divided and ligated. The division of the nerve would appear to be of no consequence. In the present group of cases, it has in each case been subject to stimulation before division, and activity of the rectus muscle has never been observed; it may reasonably be assumed that the fibres are sensory in type, being distributed to muscle and peritoneum.

This neuro-vascular bundle having been divided, the *fascia transversalis* is cut along the lateral border of the rectus muscle, and the edges of the wound are gently retracted. Careful dissection with gauze in the extraperitoneal tissue at the lower end of the wound will quickly reveal the hernial sac and canal.

Figure V gives a diagrammatic representation of the exposure at this stage and it is obvious that the major points of difficulty are all readily accessible. If desired, the sac and its contents may be readily opened through the lower end of the incision, below Poupart's ligament. Any difficulties experienced at the neck of the sac can be dealt with under vision by division of Gimbernat's ligament, without any danger to either bladder or abnormal obturator artery, should that vessel be present. Further, should it be necessary to open the peritoneal cavity in order to control bleeding from vessels in the omentum or to perform a resection of bowel, this is simply done by opening the peritoneum under the upper end of the incision, when adequate access is assured.

Finally, the sac and its contents having been dealt with as the circumstances demand, a little gauze dissection in the region of the femoral canal will clearly display the canal and will enable the surgeon to perform any type of repair with which he is familiar. The wound may be rapidly closed in layers, interrupted absorbable sutures being used for the muscle layers and linen for the skin.

Discussion.

The present method of approach has been found of particular value when dealing with the femoral hernia presenting as an acute surgical emergency. Most surgeons have had the experience of an escape of bowel of doubtful viability into the peritoneal cavity when operating on a small femoral hernia by the inguinal route. Moreover, although a resection of the small intestine is possible via the inguinal approach, there are always difficulties due to lack of adequate space in the incision in which to carry out the necessary manœuvres. Further, during the repair of the femoral canal—that all-important structure—the external inguinal vein is seen only over a small part of its length, and it is difficult to assess the degree of occlusion of the vein produced by the repair.

When the present method of exposure is used, the external iliac vein may be demonstrated by dissecting away the loose areolar tissue on its medial aspect. Usually, however, this step is not necessary, since in most cases the vein may be seen through its surrounding connective tissue sheath and left undisturbed.

On theoretical grounds an objection may be raised to any incision along the lateral border of the rectus, in that denervation and atrophy of the rectus muscle may follow such a procedure. However, as has been stated previously, only one neuro-vascular bundle has been encountered in this approach, and evidence obtained from stimulation of that bundle would suggest that the nerve is of sensory type. In one case opportunity was afforded to inspect the lower end of the rectus muscle three weeks after repair of the femoral hernia.

This patient, a man, aged fifty-six years, presented with a strangulated femoral hernia, and during the post-operative period developed acute retention of urine due to prostatic hypertrophy. Twenty days after his initial operation he was subjected to suprapubic prostatectomy, and during the approach to the prostate the rectus muscle on the side of his hernia repair was inspected. It appeared normal, contracted readily, and gave no evidence of denervation following division of the neuro-vascular bundle described above.

McEvedy (1950), in describing the operation, refers to 60 cases in which repair was carried out by this route with excellent results. He points out that the method is of great value in the uncommon case in which a patient, having previously had a repair of an inguinal hernia, presents with a strangulated femoral hernia on the same side. The present writer has used the approach in 18 cases; these consisted of seven examples presenting as surgical emergencies and 11 as elective procedures. No difficulties have been encountered at any stage during the performance of the operation, which can be completed in a relatively short space of time. The only post-operative complication has been the occurrence of the case of acute retention of urine mentioned above. Wound healing has been normal, and there have been no examples of infection.

Finally, whilst it is obvious that this method of approach is not called for in all cases of femoral hernia, it is considered that it will form a useful addition to the tactics of the surgeon in planning his approach to the femoral canal.

Summary.

1. A brief review of the evolution of the surgery of the femoral canal is given.

2. An extraperitoneal approach to the femoral canal which is seldom used is described.

3. The main advantages of this approach are as follows: (*a*) it affords adequate exposure for any intraperitoneal manipulations found to be necessary during operation; (*b*) it removes any danger of damage to the bladder or to the occasional abnormal obturator artery during repair of a femoral hernia, by affording adequate exposure; (*c*) it enables the surgeon to visualize simultaneously the femoral sac, femoral canal and intraperitoneal contents of the hernia when operating in an emergency; (*d*) it gives excellent access to the femoral canal for purposes of repair.

Acknowledgements.

I wish to thank Mr. Paul Jones and Mr. D. R. Leslie, of the Royal Melbourne Hospital, for permission to operate on these patients.

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MICROGASOMETRIC APPARATUS FOR RAPID ESTIMATION OF THE BLOOD OXYGEN CONTENT.

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ESTIMATION of the oxygen content of blood samples is important in the measurement of cardiac output during cardiac catheterization. Knowledge of the oxygen content of the blood in the peripheral vessels is also of value in the investigation of many circulatory abnormalities.

The gasometric method of Van Slyke and Neill (1924) has a high degree of accuracy, but estimations are time-consuming and require considerable training and skill. The photoelectric methods derived from that of Millikan (1933) have the disadvantage that the instruments used are complex and expensive; but they are very satisfactory for repeated estimations.

The purpose of the present investigation was to devise a gasometric apparatus which would be simple to make and to use, and at the same time give results rapidly and with considerable accuracy. The method described appears to meet these requirements.

Apparatus.

The apparatus consists of a uniform capillary tube 1·21 millimetres in internal diameter with a glass tap two centimetres from the upper end (Figure I). The length of capillary tube below the tap is 10 centimetres. The capillary expands above into a cup 5·7 millimetres in diameter for two centimetres, with a further expansion above holding six millilitres to act as a reservoir.

At the lower end of the capillary tube is an extraction bulb of seven-millilitre capacity with a narrowed apex. This is connected to a side tube six millimetres in diameter, lying alongside the capillary tube, and to a syringe filled with mercury.

The whole apparatus is mounted on a grooved "Perspex" sheet and held in a stand. Mounted behind the capillary tube is a graduated scale for measuring the volume of the gas bubble. The cup at the upper end of the capillary tube has a mark etched at 0·25 millilitre. The volume of blood required can be computed from the internal diameter of the capillary tube and the size of the scale units. In this case 0·245 millilitre was required. A blood pipette of this volume was constructed, the end of which was ground to fit exactly into the end of the capillary tube.

The diameter of the capillary tube, the dimensions of the scale units and the volume of the blood sample can obviously be varied to suit individual requirements so long as the relation between them is preserved. The apparatus can therefore be easily constructed from material at hand in any laboratory.

Reagents.

The reagents are those used by Roughton and Scholander (1943)—namely, caprylic alcohol, a ferricyanide reagent, acetate buffer, 45% urea solution, 10% sodium hydroxide solution, and pyrogallol solution.

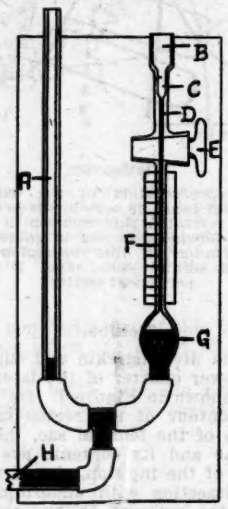

FIGURE I.

Diagram showing the apparatus. A, side tube; B, reservoir; C, cup; D, capillary tube; E, tap; F, scale; G, extraction bulb; H, to syringe.

The ferricyanide reagent contains 12·5 grammes of potassium ferrocyanide, three grammes of potassium bicarbonate and 0·5 gramme of saponin made up to 50 millilitres with distilled water. The acetate buffer contains 70 grammes of sodium acetate ($NaC_2H_3O_2.3H_2O$) dissolved in 100 millilitres of water, to which 15 millilitres of glacial acetic acid acid are added. The pyrogallol solution contains 15 grammes of powdered pyrogallol added to 100 millilitres of 20% sodium hydroxide solution.

Procedure.

The procedure is as follows.

The 20 millilitre syringe is filled with clean dry mercury and connected to the apparatus as shown in Figure I. With the tap open, the whole apparatus is filled with mercury to the top of the capillary tube. Ferricyanide reagent is added to the cup to the mark at 0·25 millilitre. Two drops of caprylic alcohol are added to the cup. By withdrawing the plunger of the syringe, the level of mercury and ferricyanide solution is lowered until the caprylic alcohol just enters the capillary tube. A sample of blood is transferred to the pipette without contact with air. The ground tip of the pipette is placed in the opening of the capillary tube below the surface of the caprylic alcohol; then the plunger of the syringe is withdrawn until the blood is all withdrawn from the pipette into the capillary tube. Three drops of

45% urea solution are added to the cup and drawn down into the capillary tube; 0·25 millilitre of the acetate buffer solution is added to the cup and drawn down into the capillary tube. The tap is closed. The mercury level in the side tube is lowered below that in the extraction bulb by withdrawing the plunger of the syringe.

The apparatus on its "Perspex" backing is unclamped from the stand and, held vertically, it is shaken vigorously from time to time for two minutes. As gas is evolved the mercury level in the side tube rises. By withdrawal of the plunger of the syringe the pressure in the extraction bulb can be kept below atmospheric pressure during evolution of the gases.

After two minutes both the small and the large cups are filled with 10% sodium hydroxide solution. The mercury level in the side tube is lowered below that in the bulb and the tap is opened. The sodium hydroxide solution then flows down into the extraction bulb, absorbing the carbon dioxide and leaving a small bubble consisting of oxygen and nitrogen, which is pushed up into the capillary tube by pressure on the plunger of the syringe. Its volume (V_1) is then read on the scale.

Excess sodium hydroxide is removed from the reservoir by suction and the cup is filled with pyrogallol. This is then drawn down the capillary tube, the bubble of gas being taken with it, until the capillary tube is filled with pyrogallol. The gas bubble is then raised again into the capillary tube and the carbon dioxide is absorbed by running the bubble several times up and down the tube filled with pyrogallol. The volume is again read (V_2).

A blank determination should be carried out, the blood being omitted, to determine the amount of oxygen dissolved in the reagents (V_3). Thus the oxygen content of the original sample is $V_1 - (V_2 + V_3)$. It has been found that the oxygen content of the reagents remains constant from hour to hour, so that only one blank determination is necessary with each series of blood analyses. The time required to carry out each determination is four minutes.

Cleaning the Instrument.

When an estimation has been carried out, the rubber tube is removed from the syringe and the mercury and solutions are allowed to pour into a beaker. By running water through the apparatus by way of the tube to the syringe for a few minutes, all traces of the reagents used are washed away. The apparatus is then rapidly dried by alcohol with air suction.

Discussion.

The results obtained by means of this method have been compared with those obtained with the manometric Van Slyke apparatus, and have been found to agree. Repeated estimations with the new apparatus give results which vary from the mean by not more than ± 0·15 volume *per centum* of oxygen. The time required to carry out each estimation is approximately four minutes.

The side tube is not just a manometer. At no time during an estimation is a pressure reading made. All measurements of gas volume are made with the tap open, so that the pressure on the gas bubble during a reading is the atmospheric pressure *plus* five centimetres of water. This side tube makes it possible for the operator to ascertain that the pressure in the extraction bulb is less than atmospheric pressure before the tap is opened, so that the reagents will pass into the capillary tube instead of the gases escaping. It also makes it easier to control the position of the bubble of gas in the capillary tube. The diameter of the side-tube is five times greater than that of the capillary tube, so that only one twenty-fifth of the amount of mercury delivered from the syringe is actually utilized in the displacing of the gas bubble up the capillary tube. By this means the bubble can be accurately and easily controlled in the capillary tube by relatively coarse movements of the plunger of the syringe.

To obtain a high degree of accuracy, the volume of oxygen should be converted to standard temperature and pressure and a correction made for the aqueous vapour pressure. This degree of accuracy is not usually required for clinical purposes.

The technique can be rapidly learnt, and accurate results can readily be obtained by a technician who is able to devote only part of his time to this work. It would therefore appear to be very suitable for use in smaller centres, where the small number of estimations carried out would not justify the considerable expense involved in the use of photoelectric equipment.

Summary.

A microgasometric apparatus for determining the oxygen content of blood samples is described. The volume of blood used is 0·245 millilitre, the time required to carry out an estimation four minutes and the error not more than ± 0·15 volume *per centum*. The apparatus can be constructed from materials at hand in any laboratory.

Acknowledgements.

The writer is indebted to Professor F. H. Smirk for helpful criticism during the preparation of this paper. The expenses of the investigation were defrayed in part by the Medical Research Council of New Zealand.

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INTERCURRENT INFECTION WITH TOXOPLASMA: ORGANISMS FOUND IN THE BONE MARROW OF A PATIENT WITH ADVANCED RETICULOSARCOMA.

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HUMAN INFECTION with the protozoon toxoplasma has received considerable attention in the world literature over the past four years (Wyllie *et alii*, 1950; Stuermer *et alii*, 1951; Winsser, 1952; Wollheim, 1952; Cole *et alii*, 1953; Armstrong and McMurray, 1953). The eight recorded cases of congenital toxoplasmosis (Robertson, 1946; Edmonds, 1949; Jack, 1952; Hertzberg, 1952; Kerkenezov, 1952) provide evidence that human infection also occurs in Australia.

The subject has been well reviewed by Sabin and his colleagues (1952) in America, and by Hertzberg (1952) in this journal. Knowledge at present available indicates that toxoplasma is a single immunological species of protozoon which occurs widely amongst wild and domestic animals. The gondi, rabbit, dog, mole, pigeon, mouse, rat, squirrel, guinea-pig, wombat, baboon, vole, canary, chimpanzee, sheep, cat and chinchilla have all been found to harbour the organism (Prior *et alii*, 1953). Its occurrence in the hare has been thought to be of importance in Denmark (Christianssen and Siim, 1951), and a recent American report states that the organisms may be found in the milk, fæces and sputum of infected cattle (Sanger *et alii*, 1953).

In Australia toxoplasma has been found in rabbits, sheep, cats and dogs (Wickham and Carne, 1950), but as yet no extensive animal surveys have been made.

Although so many animals harbour the organism, the evidence points to the dog as a likely source of infection of humans (Otten *et alii*, 1951; Christianssen and Siim, 1951; Cole *et alii*, 1953).

Infection in humans takes a number of forms. Probably the greatest number of infections are asymptomatic, as may be deduced from skin test surveys with toxoplasmin (Fisher, 1951; Stuermer *et alii*, 1951). However, infection during pregnancy, while producing no significant symptoms

[1] Working with the aid of a grant from the National Health and Medical Research Council of Australia.

in the mother, may result in the child being born with necrotizing encephalitis, later shown as scattered cerebral calcification. Infection in older children may result in severe encephalitis or even in fatal generalized disease (O'Reilly, 1954). Infection of adults, although relatively rare, is being reported with increasing frequency and may take a variety of forms (Pinkerton and Henderson, 1941; Wollheim, 1952; Franke and Horst, 1952; Kass *et alii*, 1952; Sexton *et alii*, 1953; Prior *et alii*, 1953). These include: (i) asymptomatic infection; (ii) encephalitis, encephalomyelitis or meningitis; (iii) septicæmia, with a rash similar to that of typhus fever; (iv) skin lesions similar to those of *erythema nodosum* and accompanied by lymph-node enlargement. Combinations of these symptoms may occur, as in the case of Syverton and Slavin (1946), who found toxoplasma in a piece of gastrocnemius in a tailor who was suffering from diarrhœa, muscular pain, colic and skin macules.

The diagnosis may be established by the isolation of the organism and its cultivation in the chick embryo (McFarlane and Ruchman, 1948) or the mouse. Other tests with varying degrees of reliability are the dye test, complement-fixation test and toxoplasmin skin test (Sabin *et alii*, 1952). The knowledge that human infection with toxoplasma may and probably frequently does occur without producing symptoms (Prior *et alii*, 1953) requires the results of these tests to be interpreted in the light of the clinical picture.

Since toxoplasma has been demonstrated in animals in Australia, and evidence of toxoplasma infection has been found in man, it is probable that human infection is not a rarity in this country. For this reason this report draws attention to organisms morphologically resembling those of toxoplasma which were found in the bone marrow biopsy of a patient with advanced reticulosarcoma.

Clinical Record.

The patient, a male, aged sixty-seven years, who had lived in Australia all his life, presented with loss of weight and retrosternal and epigastric pain. He was found to have a large tumour mass in the epigastrium. Portion of this was excised at laparotomy, and histological examination showed it to be composed of masses of reticulum cells, many of which were necrotic (Figure I). The appearances were those of a reticulum-cell sarcoma, and the patient was treated with deep X-ray irradiation. He became anæmic, and since radioactive phosphorus therapy was contemplated, a marrow biopsy was performed on the right iliac crest. This showed a severe degree of hypoplasia affecting all elements; there was a relative increase of plasma cells amounting to 15% of the total number of nucleated cells. In several films unusual organisms resembling protozoa were seen, occurring singly or in a clump. No furtner therapy was given. He was discharged and readmitted to hospital in congestive cardiac failure. On this occasion marrow biopsy was again performed, the material was carefully examined, and culture was attempted on artificial media and on the chorio-allantoic membrane of the developing chick embryo. However, no further organisms were noted and the attempts at culture were unsuccessful. He died thirteen days after his admission to hospital.

Post-mortem examination revealed old apical scars in both lungs. Masses of white friable tumour tissue diffusely infiltrated the anterior triangle of the neck and the mediastinum, and surrounded the duodenum and the upper part of the jejunum. Enlarged lymph nodes elsewhere in the body were soft, translucent and at times necrotic. The marrow appeared normal. Microscopic examination of the tumour tissue showed it to resemble the biopsy material. No organisms resembling toxoplasma were seen in the lymph nodes, marrow, lung or brain, despite careful search.

The Organisms.

The organisms, which were noted during life in air-dried, Leishman-stained films of the bone marrow, occurred singly (Figures II and III) or in a cluster (Figure IV). They varied slightly in size, averaging 5μ to 6μ in length and 2μ in width. They tended to be crescentic (Figures II and III); the cytoplasm stained pale blue, and in some cases was blunt at one end and pointed at the other. The nucleus occupied the full width of the organism and stained bright red. Morphologically the organisms resembled *Toxoplasma gondii*.

Discussion.

In the absence of actual isolation of the organism, the diagnosis of toxoplasmosis rests largely on clinical, radiological and serological grounds. In the present case direct proof by the cultivation of toxoplasma is also lacking, and the evidence that the organisms seen were those of toxoplasma is purely morphological.

The patient's general condition in this instance was such that minor symptoms due to transitory infection with toxoplasma would not have been noted. However, the case is presented as one of chance intercurrent infection occurring in a patient with reticulosarcoma. It is not suggested that the infection bore any more than chance relation to the reticulosarcoma, although a closer relationship with malignant lymphoma has been suggested for infection with the fungi histoplasma (Murray and Brandt, 1951) and cryptococcus (Symmers, 1953).

Summary.

1. Toxoplasma infection in humans is briefly discussed.

2. The possibility of significant incidence in Australia is suggested.

3. Intercurrent infection with toxoplasma has been presumed in a patient with advanced reticulosarcoma after the finding in the bone marrow of organisms of appropriate morphology.

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ILLUSTRATIONS TO THE ARTICLE BY E. S. FINCKH.

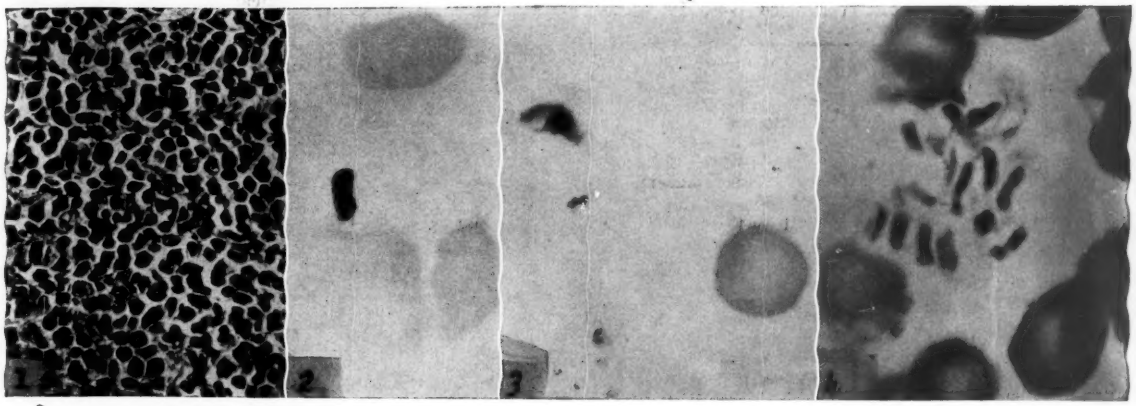


FIGURE I: Biopsy of a lymph node from a male patient, aged sixty-seven years. The section shows diffuse reticulum cell sarcoma; no toxoplasma was found despite careful searching. The patient died three months later when the reticulosarcoma was widespread. (Hæmatoxylin and eosin stain, × 260.) FIGURE II: Isolated organisms morphologically resembling *Toxoplasma gondii* obtained from the bone marrow. The nucleus occupies the full width of the organism. (Leishman stain, × 2000.) FIGURE III: Isolated organisms morphologically resembling *Toxoplasma gondii* obtained from the bone marrow. The nucleus occupies the full width of the organism, which is seen to have a blunt and a sharp end. (Leishman stain, × 2000.) FIGURE IV: A cluster of similar organisms obtained from the same patient. The preparation is an air-dried film of the bone marrow. (Leishman stain, × 2000.)

ILLUSTRATIONS TO THE ARTICLE BY FRIEDA PLARRE AND A. MURRAY CLARKE.

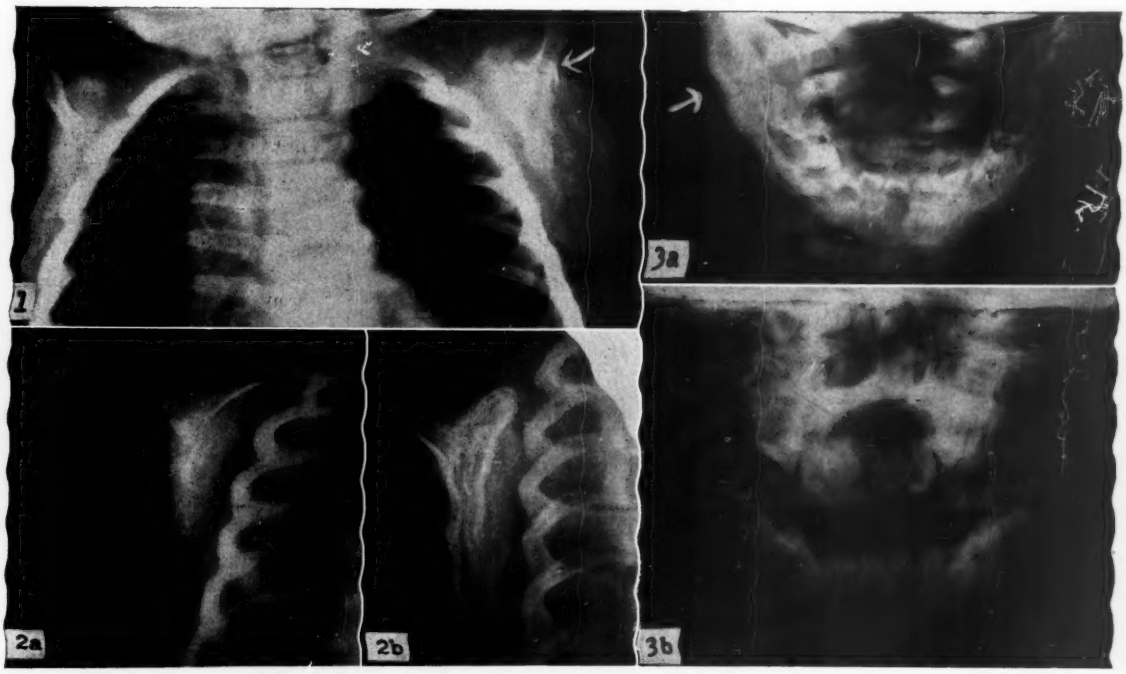
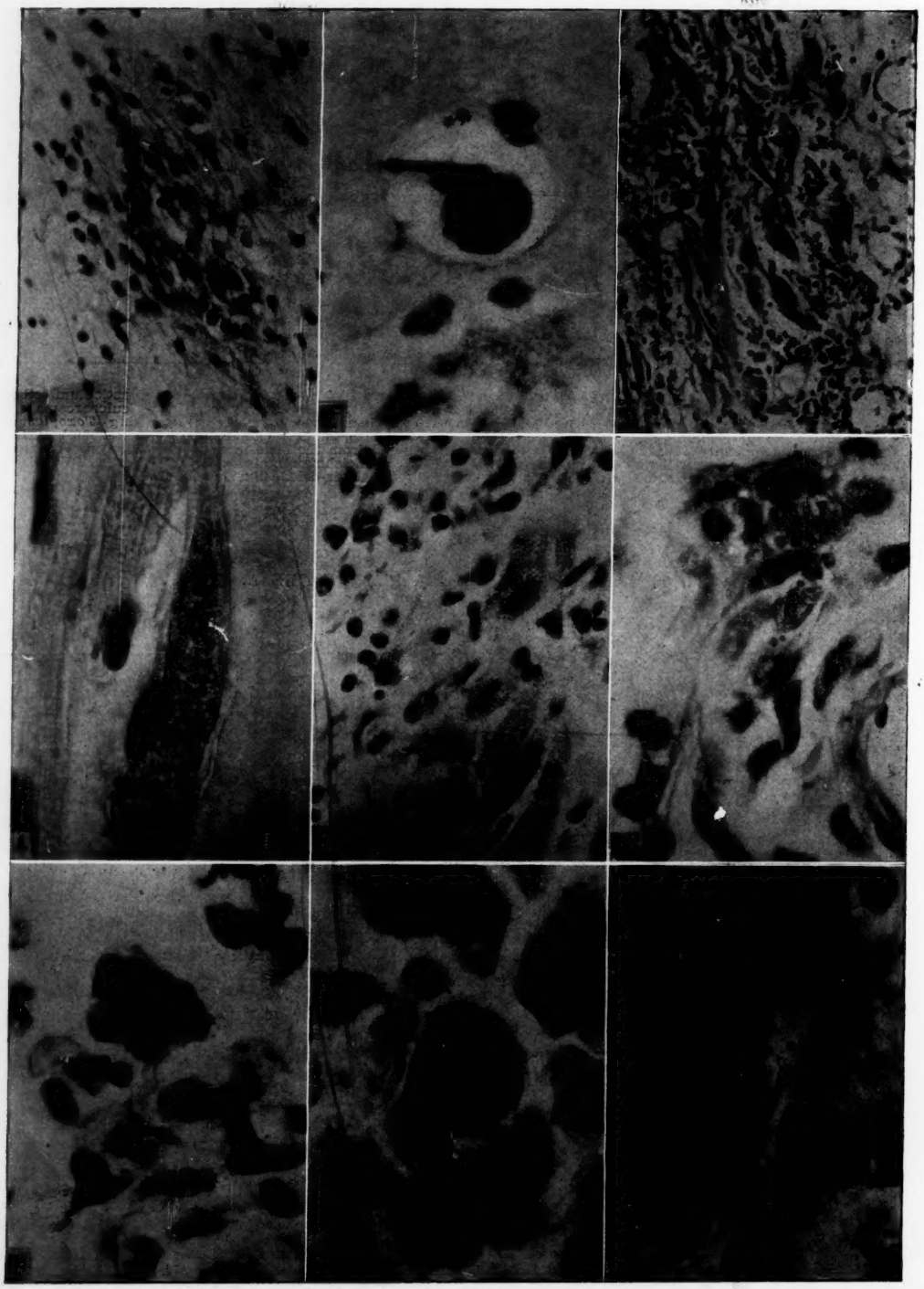


FIGURE I.—Left scapula at age of ten weeks. FIGURE II.—Lateral view of left scapula: (*a*) at age of eight weeks, (*b*) at age of ten weeks. FIGURE III.—Mandible: (*a*) at age of twelve weeks; (*b*) at age of five months.

ILLUSTRATIONS TO THE ARTICLE BY M. J. J. O'REILLY.



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Reports of Cases.

REPORT OF A CASE OF INFANTILE CORTICAL HYPEROSTOSIS.[1]

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Historical Review.

IN 1945 Caffey and Silverman reported four cases and gave the name to the new syndrome of infantile cortical hyperostosis. Since then increasing numbers of cases have been reported, until February, 1954, when Sidbury reported 10 cases, bringing the total number of reported cases to 69.

In Australia the only case to be reported is that described by Rischbieth, of Adelaide, in May, 1952. The subject of this report is the first case of infantile cortical hyperostosis to be recognized at the Royal Children's Hospital, Melbourne. The clinical picture of the syndrome is characteristic, and awareness of its existence will result in more cases being diagnosed.

The Clinical Picture.

The onset is usually within the first six months of life with the development of multiple palpable and visible swellings in the limbs and mandible accompanied by relatively mild general symptoms.

The course is protracted but self-limited, extending over several months. The swellings are at first in the deeper muscle groups overlying the bone swellings, which develop later and persist longer.

Caffey states that the commonest sites for involvement are the mandible, ulnæ and clavicles, although in the illustrations given of most cases the swellings of the long bones appear more spectacular, for they are easier to demonstrate radiologically. These swellings are nearly always multiple but not symmetrical.

The bone swellings consist of periosteal elevations, which may surround a segment of the shaft, or even envelop the whole shaft as far as the metaphysis—very aptly described as "cloaking" of the bone. They never extend beyond the epiphyseal line, but as more subperiosteal bone is laid down over the old cortex, very hard and extensive swellings may result, before resolution finally begins its slow course with eventual restoration of normal shape and structure of the bone in six to twelve months.

Clinically the swellings may be tender, but often they exhibit no tenderness at all. They are never red or hot. Apparent paresis of the affected limb is observed. The general symptoms are usually mild in proportion to the extent and persistence of the swellings, consisting of intermittent fever, leucocytosis and raised blood sedimentation rate. In more severe cases anæmia and debility may occur. In four of the 60 reported cases, sudden and unexpected death took place without very adequate post-mortem explanation of the cause of death.

The shortest duration of the disease is about three months, but remissions and relapses with new crops of swellings may occur for up to twelve months or two years. With few exceptions these babies make a complete recovery.

Case History.

A. was delivered in a country hospital with the aid of forceps but without any difficulty. No bruising was noted, and all movements were normal. When he was four weeks old his mother noticed that he would not use his left arm. She did not think that he was in pain—his arm could be moved by others after he stopped moving it himself. He could always move his fingers, wrist and elbow.

His arm was therefore bandaged by his side for two weeks, and he appeared to recover.

When he was eight weeks of age the arm became limp again and he was more irritable. A tender lump was noticed in the region of the left scapula for the first time. X-ray pictures were taken and the appearances reported as normal, but in retrospect these showed periosteal cuffing behind the glenoid region.

The swelling increased in size in spite of a week's course of penicillin.

When he was ten weeks old he was referred to the Royal Children's Hospital. He was a well-looking baby with a large swelling over the left scapula, firm and non-tender. There was no limitation of movement in the shoulder joint. He was afebrile and the result of a Wassermann test was negative. X-ray examination showed enlargement of the left scapula with extensive masses of subperiosteal bone laid down on the subscapular, infrascapular and suprascapular surfaces, as well as a smaller degree of periostitis extending over the acromion process (see Figures I and II).

Lack of history of sufficient trauma excluded the diagnosis of ossifying hæmatoma. There was no history of soreness or abscess of the mother's breast or infective lesions of the child's skin or umbilicus, or pyrexia to support a diagnosis of osteomyelitis. The mass was considered to be due either to osteomyelitis or to a malignant bone condition, and a biopsy was carried out. Subcutaneous tissue and muscle appeared normal. Dr. A. L. Williams reported on the piece of bone removed that there was no evidence of malignancy, the appearance being that of an osteoma. The baby was accordingly discharged from hospital back to the country.

A review of the X-ray films then suggested the diagnosis of infantile hyperostosis. The clear-cut outline, the periosteal swelling with absence of any bone destruction was against malignant disease of bone. The involvement of all surfaces of the scapula would make a single hæmatoma anatomically impossible, and multiple hæmatomata would be unlikely without extensive bone trauma.

The extent of periostitis without any focus of bone destruction after such a long course, together with the biopsy findings, excluded osteomyelitis.

The course of the condition, commencing as a large periosteal cuff adjacent to the glenoid fossa and rapidly spreading to envelop and "cloak" the whole bone, except the articular surface, was characteristic of infantile cortical hyperostosis, together with the fact that the scapula, though infrequently the site of focal bone lesions, is very often the site of swelling in young infants with infantile cortical hyperostosis. Fairbank quotes one case in which a radical excision of the scapula was carried out for a mistaken diagnosis of malignant disease of bone.

One difficulty in making a diagnosis in this case was that up to this stage only one swelling had been noted, and the multiplicity of lesions is a feature of infantile cortical hyperostosis. A radiological survey of the skeleton

[1] Read at a meeting of the Pædiatric Society of Victoria on July 14, 1954.

a fortnight later revealed involvement of the angle of the mandible (see Figure IIIa).

This showed itself in slight thickening and increased density of the right side of the mandible, which in the oblique view was localized mainly around the angle of the mandible and the coronoid process. When examined after five months' time the baby was quite normal clinically, and X-ray appearances of the left scapula and mandible were normal again.

Comment.

The diagnosis of the condition of infantile cortical hyperostosis depends on the clinical and radiological demonstration of multiple bone swellings having their onset during the first six months of life.

Awareness of this condition enables a good prognosis to be given, and the importance of searching for other areas of skeletal involvement by X-ray examination, particularly of the mandible, clavicles, ulnæ and ribs, is evident in making a diagnosis. It has been stated that mandibular involvement is usually found at some stage of the disease if carefully looked for. Bone biopsy is unnecessary for diagnosis, though of interest in pathological study.

The ætiology of infantile cortical hyperostosis is unknown. Some favour a theory of virus infection, while others favour a congenital origin. One case has been diagnosed *in utero* in the thirty-first week of pregnancy. It seems likely that as the condition is looked for and more accurately diagnosed during this age period of early infancy, it may become apparently less rare as shown by the increasing number of cases reported in the literature.

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ACQUIRED TOXOPLASMOSIS: AN ACUTE FATAL CASE IN A YOUNG GIRL.

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HUMAN cases of toxoplasmosis have been reported from most Australian States (Robertson, 1946; Edmonds, 1949; Jack, 1952; Hertzberg, 1952; Kerkenczov, 1953), but not hitherto from Queensland. These Australian cases and the majority of cases in other countries have been of the congenital type, the infection occurring *in utero*, presumably by transplacental transmission, and giving rise to disseminated encephalomyelitis and chorio-retinitis.

On the basis of skin tests and serological investigations it is believed that infection commonly occurs in extra-uterine life; but the majority of persons so infected display few or no symptoms. Occasionally a severe and even fatal illness may result with involvement of many organs (Kass *et alii*, 1952). The case to be described falls within this category, the diagnosis having been made on histological and morphological criteria.

Clinical Record.

The patient was an illegitimate female child, aged ten years. Her mother was reported to have been perfectly well during the pregnancy, and subsequently married and gave birth to three normal healthy children. The birth of the patient was uneventful and she progressed normally. She was bright and intelligent and is said to have been above average in her school work. At the age of seven years she was hit on the leg by a stone, and this area became infected. A sore later developed on the lower lip and subsequently the cervical lymph glands became enlarged. Three months after the injury she was admitted to hospital with generalized enlargement of lymph glands and with a history of vomiting, malaise, lassitude and occasional epistaxis of four days' duration.

On examination the patient was found to be a well-built little girl with numerous large cervical, axillary and inguinal glands, which were discrete, rubbery and moderately tender. The liver and spleen were not palpable. The teeth were badly decayed. The temperature was not raised. The red blood cells numbered 2,000,000 per cubic millimetre and the hæmoglobin value was 55%. The white cells numbered 10,800 per cubic millimetre, 74% being neutrophile cells and 26% lymphocytes. A Mantoux test produced a negative response.

A gland from the right inguinal region was removed for biopsy and a diagnosis of reticulosarcoma was made. A course of deep X-ray therapy was given; during this the child developed right basal pneumonia, which resolved in about ten days.

At the time of the patient's discharge from hospital the glands were considerably reduced in size. She continued to attend for deep X-ray therapy as an out-patient for two years, and during this time remained well and attended school as usual. After treatment had been discontinued she was examined periodically by the radiotherapist, and when she was last examined two months before her death no glands were detectable.

The final illness was of one week's duration, during which she suffered from intermittent headache and some malaise. Two days before death she vomited several times, but had no diarrhœa. The following day she was taken to hospital, where no significant abnormalities were noted and she was not admitted. Shortly after her return home transient cramp or paralysis of the right leg occurred. On the day of her death she was very weak and stayed in bed. She complained of some tightness in the chest and vomited once. However, she appeared to be mentally alert up to the time of her death, which occurred suddenly at 6.30 p.m.

Post-Mortem Findings.

Autopsy was performed sixteen hours after death. The body was that of a well-nourished young girl, and showed obvious pallor of the skin and mucous membranes. The brain was heavy (1525 grammes) and showed superficial congestion, but otherwise appeared normal. The trachea and bronchi contained abundant frothy watery fluid, and the lungs were voluminous, pale and very œdematous. About 100 millilitres of clear, pale yellow fluid were present in each pleural cavity. The heart was of normal size (196 grammes), and macroscopic examination revealed no abnormality. The spleen was large (224 grammes) and firm, the cut surface being uniformly pink in colour. The liver, kidneys, suprarenals and genitalia all appeared normal. The stomach was dilated with dark green watery fluid. The mucosa of the entire alimentary tract appeared normal, and no inflammatory lesions could be detected. There were a few slightly enlarged lymph glands in the neck, the largest measuring 1·5 centimetres in length, and numerous large mesenteric and paraaortic lymph glands measuring up to 8·5 by 2·5 by 1·5 centimetres.

Salmonella typhi-murium was isolated from the small and large intestines.

Histological Findings.

Organisms morphologically similar to toxoplasma were found in abundance in the myocardium, occasionally in the cerebral cortex and lung, and very sparsely in the lymph glands and liver. None could be found in the spleen, kidneys, suprarenals or pancreas.

In the cerebral cortex small numbers of microglial nodules were scattered in the white matter (Figure I), and in association with some of these nodules groups of intracellular proliferative forms of toxoplasma could be

seen. Similar intracellular parasites were occasionally found without any surrounding reaction (Figure II). In some places mild perivascular accumulation of small round cells was noted. No encysted forms of toxoplasma could be found in any of the tissue examined.

In all sections of the myocardium a pronounced inflammatory reaction was present. Interstitial œdema and a heavy cellular exudate separated and surrounded individual muscle fibres, many of which showed varying degrees of degeneration and disintegration (Figure III). The cellular exudate consisted mainly of mononuclear cells and lymphocytes together with a few plasma cells and polymorphonuclear cells. The inflammation had also extended to the subpericardial fat in some areas, with early necrosis of individual fat cells. Proliferative forms of toxoplasma were readily found lying in masses within individual muscle fibres (Figure IV), generally unassociated with the inflammatory reaction, though sometimes the fibre lay within an inflammatory focus (Figure V). In some such foci the fibre was seen to be ruptured and a few organisms were lying free in the interstitial tissue.

In the lungs diffuse interstitial pneumonitis was present. The alveolar walls were thickened by œdema and by a cellular exudate composed mainly of lymphocytes and mononuclear cells. Many of the alveoli contained œdema fluid as well as large macrophages. A few intracellular toxoplasma organisms were seen in histiocyte-like cells lying just within (Figure VI) or at the periphery of (Figure VII) the alveolar septa.

In the liver the portal tracts were infiltrated with lymphocytes and a few polymorphonuclear and mononuclear cells. Small scattered areas of focal necrosis were distributed at random through the parenchyma. Several sections were examined, but only one small collection of toxoplasma organisms was found, and that within an apparently normal parenchymal cell (Figure VIII).

In the spleen there was a generalized cellular increase in the pulp, comprising mainly lymphocytes and mononuclear cells together with macrophages. Some scattered fibrotic nodules were seen, generally related to arterioles, where the fibrous strands were arranged concentrically around the vessels. The Malpighian corpuscles were evident, though some were reduced in size and the germinal centres were less prominent than usual. No definite toxoplasma organisms could be found.

In all lymph glands examined subacute or chronic nonspecific inflammatory changes were found. The architecture was preserved and some follicles were hyperplastic with increased phagocytosis of nuclear debris. Mononuclear cells, plasma cells, lymphocytes and a few polymorphonuclear cells crowded the sinuses and in some cases infiltrated the capsule. A moderate number of arterioles were surrounded by concentric layers of dense fibrous tissue. A few groups of intracellular toxoplasma organisms were found contained within histiocytes and lying mainly in or near the capsule (Figure IX).

No significant pathological changes were seen in the kidney, suprarenals or pancreas.

Discussion.

The diagnosis of toxoplasmosis in this case cannot be regarded as definitely proven, as it relies entirely on histological and morphological grounds and is unconfirmed by serological or cultural investigations. Nevertheless the histopathological findings seem sufficiently characteristic for the diagnosis to be regarded as highly probable and to warrant the reporting of the case under this title. Dr. J. K. Frenkel, of the University of Kansas Medical Centre, has kindly reviewed the sections and is in agreement with the designation of this case as one of toxoplasmosis.

The clinical history, the histological characteristics of the lesions found, and the absence of any encysted forms of toxoplasma all point to an acute and recently acquired infection. The child lived on a small farm and was in contact with cows (one of which was reported to be very thin and unhealthy), fowls, ducks, goats, a dog and a cat; but the possibility of any of these animals being the source of the infection could not be investigated, as a considerable period elapsed between the child's death and the establishment of the diagnosis. During this time the farm was sold, the stock were scattered and the dog and the cat had died.

It is not altogether clear what significance can be attached to the finding of *Salmonella typhi-murium* in the intestine at autopsy. Neither the symptoms nor the autopsy findings suggest a severe gastro-intestinal infection, although it is conceivable that an intercurrent salmonella infection could have increased the severity of the toxoplasmic infection and possibly determined the fatal outcome. On the other hand, it is difficult to believe that a salmonella infection played any part in producing the cerebral, the myocardial or even the pulmonary lesions, and it is not unreasonable to explain the final illness and death on the basis of myocardial failure due to the toxoplasmic myocarditis, the salmonella being relegated to the status of an incidental finding.

It is an interesting coincidence that Finckh (1954) describes the finding of toxoplasma in a patient suffering from reticulum cell sarcoma. However, the coincidence is more apparent than real, for an examination of the original lymph gland biopsy on which the diagnosis of reticulum cell sarcoma was made in the present case indicates that the diagnosis was in error, the gland showing nothing more than inflammatory hyperplasia. Several sections from this original block were examined carefully for toxoplasma without success.

Summary.

1. A case of acute fatal toxoplasmosis in a girl, aged ten years, is described.

2. Inflammatory lesions were present mainly in the myocardium and lung.

3. Organisms morphologically identical with toxoplasma were found in the myocardium, cerebral cortex, lung, liver and lymph glands.

Acknowledgements.

I am indebted to Dr. J. K. Frenkel, Department of Pathology and Oncology, University of Kansas Medical Centre, for examining sections and for his helpful comments.

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Legends to Illustrations.

FIGURE I.—Microglial nodule in white matter of cerebral cortex (iron hæmatoxylin stain, × 380).

FIGURE II.—Group of toxoplasma organisms lying within the body of a pyramidal cell (iron hæmatoxylin stain, × 1500).

FIGURE III.—Myocardium showing inflammatory reaction (iron hæmatoxylin stain, × 190).

FIGURE IV.—Collection of toxoplasma organisms in a myocardial fibre (iron hæmatoxylin stain, × 1500).

FIGURE V.—Area of myocarditis with toxoplasma in a muscle fibre (iron hæmatoxylin stain, × 625).

FIGURE VI.—Lung: an alveolar septum in which is a histiocyte containing toxoplasma organisms (iron hæmatoxylin stain, × 1500).

FIGURE VII.—Lung: histiocyte filled with toxoplasma organisms lying within an alveolus (iron hæmatoxylin stain, × 1500).

FIGURE VIII.—Liver: toxoplasma organisms lying within a normal parenchymal cell (iron hæmatoxylin stain, x 1500).

FIGURE IX.—Lymph gland: intracellular toxoplasma organisms in the capsule (Lillie's azure eosin stain, x 1500).

A FATAL OVERDOSE OF "DARAPRIM".

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IN 1953 the death was reported of a child, aged twenty months, who had swallowed about 15 tablets (each 25 milligrammes) of "Daraprim" (pyrimethamine); he developed convulsions after about three-quarters of an hour, and died two hours later (Covell, 1953). In the same paper it was reported that two other children consumed up to about 15 tablets without severe results. Also in 1953 (Abbott and Hamdi) it was reported that a child, aged three years and two months, recovered after taking 15 tablets.

On June 27, 1954, at Mumeng in New Guinea, a white girl, aged two years and four months, in excellent health, who had regularly been given "Daraprim" for malaria prophylaxis, secured the bottle and ate 16 tablets, each of 25 milligrammes (a total of 400 milligrammes) at about 11.30 a.m. At about 12 noon she vomited profusely, and her parents then found the empty bottle. The vomitus appeared to consist of ordinary stomach contents, and contained no recognizable portions of tablets. Shortly afterwards she developed prolonged, severe convulsions, and hot and cold baths were given. When the convulsions ceased she was comatose, collapsed, pale and cyanosed and almost pulseless, with short shallow respirations. Two injections of "Nikethamide" were given, without benefit, and oxygen was administered, also without benefit. She died shortly after 2 p.m.

Discussion.

In the paper by Covell (1953) mentioned above, the following statement was made: "These cases underline the fact that the drug has a relatively attractive taste, and therefore needs to be carefully locked up." Actually, this is not the real solution. In malarious areas the taking of some anti-malarial drug is essential, especially in the case of children. It is accordingly most important that the children be made familiar with the drug, and taught to take it willingly. In most tropical households the drug in use is as familiar on the table as the cruet, and in the ordinary course of domestic routine it is equally as likely to be left about as the cruet is. Moreover, a bitter taste is no bar to a child's eating tablets with which it is familiar. In 1950, also at Mumeng, a girl aged three years ate 20 tablets (each 100 milligrammes—a total of two grammes) of "Paludrine" (proguanil) (Gunther, 1951). She vomited after half an hour, was rather collapsed for another hour, passed almost pure blood in her urine for three days, and then recovered, without any subsequent kidney damage. "Paludrine" has an incomparably more unpleasant taste than "Daraprim"; yet this child ate 20 tablets of her own accord, and most children take it without trouble.

I would say that it is almost impossible to keep anti-malarial drugs always out of reach of an enterprising child, and that the better safety measure (while, of course, an attempt is made to keep all drugs away from children) is to choose the less toxic and less dangerous drug for household use.

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ACUTE APPENDICITIS IN PREGNANCY: A REPORT OF THREE CASES.

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THE incidence of acute appendicitis in pregnancy has been variously estimated at from one in 1000 to one in 2000 cases. The occurrence of the following three cases within four months suggests that they may be of sufficient interest to others to warrant recording.

Case I.

Mrs. A., aged twenty-four years, was twenty weeks pregnant when admitted to hospital on April 16, 1953, from the casualty department of another hospital. This was her third pregnancy, and she gave a history of jaundice at the age of eighteen years and of an attack of pyelitis in September, 1952. She had been well until the evening of April 14, 1953, when she developed colicky epigastric pain soon after her evening meal, which persisted for eight hours and then changed to a constant lower abdominal pain; this steadily increased in intensity and became localized to the right side. Vomiting of food and fluid had been present for thirty-six hours. She had had three loose motions on the day before her admission to hospital, and also some frequency of micturition, but without burning or scalding. She had had no previous similar abdominal pain.

The patient was a pale, sick-looking woman with a dry, coated tongue. Her temperature was 100° F. and her pulse rate 100 per minute. There was generalized abdominal tenderness with maximum tenderness and guarding at McBurney's point. Rovsing's sign was present, and pain was felt on the release of pressure over the right iliac fossa. Bowel sounds could be heard. Vaginal examination disclosed a uterus enlarged to the size of a twenty weeks' pregnancy. The white blood cells numbered 13,400 per cubic millimetre, 85% being neutrophile cells, 7% lymphocytes and 8% monocytes. A catheter specimen of urine contained numerous pus cells and two or three red blood cells per high power field in the centrifuged deposit. Attempted culture of microorganisms from the urine was unsuccessful.

Appendicectomy was performed five hours after the patient's admission to hospital through a generous McBurney's incision, and an acutely inflamed retrocaecal appendix was removed by the retrograde method with some difficulty. It was considered at the time that performance of this operation through a high paramedian incision would have been considerably more difficult. The patient was given morphine sulphate, a quarter of a grain, when conscious, and one-sixth of a grain thereafter at intervals of six hours for twenty-four hours. Chemotherapy was commenced with streptomycin, 0·5 gramme twice daily and soluble penicillin, 300,000 units every six hours. The temperature fell to normal after twenty-four hours, and the convalescence was uneventful, the patient being discharged from hospital on the tenth post-operative day.

Case II.

Mrs. B., aged twenty-four years, was admitted to hospital on the evening of April 27, 1953, when she was approximately fourteen weeks pregnant. In 1952 she had undergone a right salpingectomy for a ruptured tubal gestation. She gave a history of abdominal pain of twelve hours' duration, at first localized to the area around and above the umbilicus, but now of a generalized nature. She had been nauseated all day, but had not vomited, and the bowels had opened normally once in the day.

Examination showed the patient to be a pale, anxious-looking woman not in obvious pain. The tongue was clean and moist, the temperature 98·4° F., and the pulse rate 98 per minute. There was definite tenderness localized to McBurney's point, and the bowel sounds appeared to be reduced. Vaginal examination showed the uterus to be enlarged to the size of a fourteen weeks' pregnancy.

Lower abdominal pain persisted throughout the night, and the patient vomited once. By the next morning the tongue was coated and the breath somewhat foul. There was now pronounced tenderness in the right iliac fossa and slight localized tenderness in the left iliac fossa. Her temperature was 99° F. and her pulse rate 94 per minute. The white blood cells numbered 11,500 per cubic millimetre, 69% being neutrophile cells, 14% lymphocytes, 11% monocytes and 6% eosinophile cells.

Appendicectomy was performed at 4 p.m. that day through a McBurney incision, and an acutely inflamed appendix five inches long and considerably thickened was removed. The appendix and its mesentery were œdematous, and the tip of the appendix was covered with a thick fibrinous exudate. Convalescence was uneventful, and the patient was discharged from hospital on the tenth post-operative day.

Case III.

Mrs. C., aged twenty-eight years, was twenty-two weeks pregnant in her first pregnancy when she developed central abdominal pain of sudden onset during the night of July 6, 1953. She gave a history of rheumatic fever at the age of fifteen years, having been confined to bed for two months at that time. She had been treated for chronic sinusitis by antral lavages and had suffered an occasional attack of asthma.

Examination the next morning disclosed the patient to be a small, healthy-looking woman with a slightly furred tongue and an offensive breath. Her temperature was 98° F. and her pulse rate 100 per minute. The abdomen was enlarged by a twenty-two weeks' pregnant uterus, and the whole of the lower part of the abdomen was tender and resistant, with maximum tenderness along the right side of the uterus and in the narrow triangle between the uterus and the iliac crest. The white cells numbered 30,500 per cubic millimetre, 89% being neutrophile cells, 9% lymphocytes and 2% monocytes.

Appendicectomy was performed that afternoon through a McBurney's incision. The appendix was long and acutely inflamed, the distal half being swollen to a diameter of half an inch and covered with a thick fibrinous exudate. Her convalescence was uneventful, and she was discharged from hospital on the twelfth post-operative day.

Discussion.

While the actual incidence may be difficult to assess because many patients must be operated on in whom the presence of an early pregnancy is unrecognized, there is no doubt that the peak incidence occurs from the second to the sixth months of pregnancy (Jerlov).

In large series it has been shown that less than 10% of cases occur in the last three months of pregnancy.

The symptomatology is that of acute appendicitis complicated by an enlarged uterus, which pushes the caecum and appendix upwards and outwards from the third month on (Baer, Reis and Arens, 1932). These authors have also shown by a series of X-ray studies of normal appendices in pregnancy that the appendix alters its direction from an original downward medial line until at term it runs upward and medially parallel to and some two inches below the costal margin. Tenderness and rigidity will consequently be at a higher level, and the confusion with right-sided pyelitis can be a very real problem. Generally the tenderness with pyelitis can be expected to cover a much wider area than the localized tenderness of an acutely inflamed appendix.

Treatment is surgical in all cases, and Babler's statement that "the mortality of appendicitis complicating pregnancy and the puerperium is the mortality of delay" explains the unfortunate results to mother and child when rupture or gangrene of the appendix has occurred.

Early operation carries no risk to the mother, and the incidence of abortion is not greater than normal (Twyman, Mussey and Stalker, 1940).

However, during pregnancy there is a tendency to gangrene and abscess formation some four to six times greater than in the non-gravid patient, and should perforation occur, abortion or premature labour can be expected in 50% of cases.

Adequate exposure can be obtained in all cases up to the sixth or seventh month by a generous muscle-splitting incision of the McBurney type, which must always be centred over the maximum area of tenderness and may of necessity be somewhat higher than in the non-pregnant patient. Handling of the uterus can be minimized, and indeed in most cases the uterus will not even be seen.

An observation on the so-called McBurney incision may not be out of place in this discussion. The two limiting features of this incision appear to be the width of the *rectus abdominis* muscle and the position chosen for splitting the internal oblique and transversus muscles. It has been found helpful to gauge the width of the rectus pre-operatively, and to try to assess by the position of maximum tenderness the site at which the inner layer of muscles should be split. This procedure should largely prevent the not infrequent occasions when the incision fails to give adequate exposure to the appendix, usually through being made too low and too medially in the right iliac fossa.

In the last months of pregnancy most authorities recommend a generous right paramedian incision; but I should like to urge the adoption in such cases of a transverse incision placed well to the right over the area of maximum tenderness, as being less likely to disseminate infection widely through the peritoneal cavity. Should general peritonitis be present, the adoption of such an incision, with adequate drainage and chemotherapy, seems preferable to the reported procedures of Cæsarean section with or without total hysterectomy.

Summary.

Three cases of acute appendicitis complicating pregnancy are reported. In each case appendicectomy was performed.

A short discussion of the condition is given, in which emphasis is laid on early operation and the greatly increased tendency to gangrene and abscess formation in the pregnant subject.

Finally a plea is made for the avoidance of mid-line incisions in such cases.

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Reviews.

Urological Practice. By Roger W. Barnes, B.A., M.S., M.D., F.A.C.S., F.I.C.S., and Henry L. Hadley, B.A., M.D., D.N.B., with contributions by six other authors; 1954. St. Louis: The C. V. Mosby Company. Melbourne: W. Ramsay (Surgical), Limited. 10″ × 7″, pp. 494, with 166 illustrations. Price: £6 11s. 3d.

FINE judgement is required to determine what urology should reasonably be practised by the general practitioner. R. W. Barnes and H. L. Hadley have made a most successful selection in their "Urological Practice", a book specially designed for rapid reference by the general practitioner.

The presentation is rather original in that the first section is an index of symptoms where the causes and symptomatic treatment are mentioned and references given to more details in later chapters.

These systematic descriptions are succinct, but readability has not been sacrificed for brevity. Deliberate omissions are anatomy, physiology, much pathology and references to the literature. Similarly, although the operations which might be used by a general practitioner are found in some detail,

all others are described in general terms with an appreciation of the post-operative prognosis. "Office procedures", which are more extensive than in the usual Australian practice, are explained meticulously, but the surgeon who proposes to exceed the simple cystoscopic manœuvres described is advised to obtain a treatise on cystoscopy and to practise under an experienced operator.

Other contributors have supplied chapters on sexual maladjustment, infertility, scrotal diseases, non-surgical kidney disease and differential diagnosis of abdominal pain. Excellent photographs and original line drawings materially assist the descriptive material and add to the esentially practical nature of the book. Paper, printing and indexing are all attractive, and the book is easily read and most suitable for rapid reference.

This book was prepared with the real needs of the general practitioner in mind. It fulfils its purpose admirably.

Cancer: Diagnosis, Treatment and Prognosis. By Lauren V. Ackerman, M.D., and Juan A. del Regato, M.D.; Second Edition; 1954. St. Louis: The C. V. Mosby Company. Melbourne: W. Ramsay (Surgical), Limited. 10" x 7", pp. 1202, with 725 illustrations, 23 in colour. Price: £11 16s. 3d.

IN this book the subject of cancer is presented on a broad basis—its history, its experimental production, its reaction to all forms of accepted treatment and their evaluation at the end of each chapter. There is a great number of references to the works of the many authors quoted. The illustrations are numerous and of high standard, and the experienced clinician, technician and surgeon will appreciate their true worth.

In the United States of America in 1948, 200,000 deaths from cancer were recorded, but it is pointed out that this number is no indication of the incidence of cancer, for in many cases cure is effected and in others the cancer is not the cause of death.

In 1950 there were 251 cancer detection centres in the United States of America. The cost of discovering each case of cancer is estimated at $10,000.

The authors suggest that only those who are adequately trained and qualified should have the responsibility of treating cancer, and that isolated workers should be discouraged as they are apt to perpetuate their mistakes—particularly pathologists. The bold statement is made that one in four of cancer patients is cured by surgery, X-ray or radium therapy; that one in four is dying through delay or inadequate treatment; that two in four are doomed to die unless new knowledge is obtained by research. Insistence is made that, where possible, biopsy should be carried out before the appropriate method of attack is undertaken. If surgery is decided upon radical methods should be adopted. The fast disappearing race of general surgeons will derive some satisfaction in learning that radical surgery on the neck is still advocated for buccal, tongue and late lip cancer.

The cause of cancer still remains unsolved. It is pointed out that œstrogenic compounds may initiate in some unknown way a number of neoplastic processes in tissues usually under the influence of sex hormones.

Cancer of the lung is considered primarily a disease of males, for only 10% to 15% of cases are found in females. The difference remains unexplained, and though smoking by women has become more prevalent there is no increase in cancer among them.

Workers in cobalt and uranium mines in Germany have been found to suffer a high incidence of cancer of the lung, assumed to be due to some radioactive substance. It is suggested that workers in chromate and asbestos industries should be carefully watched for lung cancer. This is particularly important to Australia at present where many uranium fields are being opened up.

Cancer in every organ of the body is discussed. The primary attack should be bold, whether by therapeusis or by surgery.

Cancer is said never to occur in a toxic goitre, though the two conditions may coexist.

It is stated that few cancers of the stomach are secondary to simple ulceration; that 90% of tumours of the appendix are carcinoids; that nearly 50% of cancers of the large bowel occur in the rectum; that two-thirds of cancers of the large bowel can be diagnosed by the finger or sigmoidoscope. Abdomino-perineal excision of the rectum is still advised for cancer of the rectum, in spite of the many advocates for preserving the *sphincter ani* when possible. It is suggested that it is better to live with a permanent colostomy than to die with a preserved sphincter.

The advisability of operating for cancer of the body of the pancreas is questioned as metastases occur early and the cures are few and far between.

Cancer of the liver is stated to be most prevalent in those races who have suffered food deficiency; it is also stated that cancer of the gall-bladder may be present in as high a proportion as 4% of gall-bladders containing stones.

Hodgkin's disease and the leuchæmias are classified with cancer.

In conclusion, the authors are to be complimented on production of this work of outstanding merit, for it contains much of interest and of value to medical men and laymen.

Books Received.

[The mention of a book in this column does not imply that no review will appear in a subsequent issue.]

"Anesthesiology: By Forty American Authors", edited by Donald E. Hale, A.B., M.D., M.S., F.A.C.S., F.A.C.A.; 1954. Philadelphia: F. A. Davis Company. Sydney: Angus and Robertson, Limited. 10½" x 7", pp. 770, with 149 illustrations. Price: £8 1s. 3d.

There are 40 contributors to this book which contains 33 chapters.

"The Child, His Parents and the Nurse", by Florence G. Blake, R.N., M.A., with a foreword by Adrian H. VanderVeer, M.D.; 1954. Philadelphia: J. B. Lippincott Company. Sydney: Angus and Robertson, Limited. 9½" x 6½", pp. 458, with one illustration. Price: 53s. 9d.

Deals with the psychology of the growing child and his emotional needs in sickness and health.

"Radiology for Medical Students", by Fred Jenner Hodges, M.D., Isadore Lampe, M.D., and John Floyd Holt, M.D.; Second Edition; 1954. Chicago: The Year Book Publishers, Incorporated. 8" x 6", pp. 440, with 106 illustrations. Price: $8.00.

Intended to give to medical undergraduate students the necessary minimum material on which they may develop a sound basic understanding of medical radiology.

"Developmental Anatomy: A Textbook and Laboratory Manual of Embryology", by Leslie Brainerd Arey, Ph.D., Sc.D., LL.D.; Sixth Edition; 1954. Philadelphia and London: W. B. Saunders Company. Melbourne: W. Ramsay (Surgical), Limited. 10" x 7", pp. 690, with 630 illustrations, some in colour. Price: £4 10s. 3d.

The book was first published in 1924; this edition has been "replanned, revised and rewritten".

"Galen of Pergamon", by George Sarton; 1954. Lawrence, Kansas: University of Kansas Press. 8½" x 5½", pp. 120. Price: $2.50.

This is one of the Logan Clendening Lectures on the History and Philosophy of Medicine.

"Textbook of Pediatrics", edited by Waldo E. Nelson, M.D.; Sixth Edition; 1954. Philadelphia and London: W. B. Saunders Company. Melbourne: W. Ramsay (Surgical), Limited. 10½" x 7½", pp. 1600, with 438 illustrations. Price: £7 2s. 6d.

First published in 1933; there are 72 contributors to this edition.

"Cancer: Race and Geography: Some Etiological, Environmental, Ethnological, Epidemiological, and Statistical Aspects in Caucasoids, Mongoloids, Negroids, and Mexicans", by Paul E. Steiner, Ph.D., M.D.; 1954. Baltimore: The Williams and Wilkins Company. Sydney: Angus and Robertson, Limited. 9" x 6", pp. 376, with 73 text figures. Price: 53s. 9d.

Concerned chiefly with the ætiological implications of the racial and geographical differences in cancer.

"Human Biochemistry", by Israel S. Kleiner, Ph.D.; Fourth Edition; 1954. St. Louis: The C. V. Mosby Company. Melbourne: W. Ramsay (Surgical), Limited. 10" x 7", pp. 746, with 98 illustrations, five in colour. Price: £3 18s. 9d.

Completely revised and largely rewritten with inclusion of much new material.

The Medical Journal of Australia

SATURDAY, DECEMBER 18, 1954.

All articles submitted for publication in this journal should be typed with double or treble spacing. Carbon copies should not be sent. Authors are requested to avoid the use of abbreviations and not to underline either words or phrases.

References to articles and books should be carefully checked. In a reference the following information should be given: surname of author, initials of author, year, full title of article, name of journal, volume, number of first page of the article. The abbreviations used for the titles of journals are those adopted by the Quarterly Cumulative Index Medicus. If a reference is made to an abstract of a paper, the name of the original journal, together with that of the journal in which the abstract has appeared, should be given with full date in each instance.

Authors who are not accustomed to preparing drawings or photographic prints for reproduction are invited to seek the advice of the Editor.

EDITORIAL RESPONSIBILITY IN RELATION TO HUMAN EXPERIMENTATION.

THE most important subject discussed at the medical journalism meeting held in connexion with the eighth General Assembly of the World Medical Association at Rome at the end of September, 1954, was editorial responsibility in relation to human experimentation. At first sight, this subject appears to be quite a simple matter and one about which not a great deal might be said. When the subject was fully explained, however, it was clear that medical editors had to accept a great deal of responsibility in publishing the reports of experiments on human beings. The subject was discussed in two sections. The first had to do with the responsibility of the man carrying out the experiments, and the second with the responsibility of the editor who published an account of them. The subject was introduced by a paper in the form of a report by Professor G. C. Heringa, Editor-in-Chief of *Medical Contact* (the Netherlands). His report was presented to the General Assembly as well as to the medical journalism meeting. Professor Heringa began by affirming that medical ethics was not the sole property of medical men, but that it formed the basis of the confidence between patient and physician which had grown through the ages and which was the property of all mankind. He declared that the medical practitioner should never forget that his private conscience and that of the world were interwoven inseparably. Like religion in its manifold forms, medicine comprised in its ethics the experience of and aspiration towards the highest form of humanity, the reflection of divine love. Hence, medical ethics had contributed to the introduction of humanistic elements into society, and also determined the general aspect and the conscience of culture. Professor Heringa quoted Albert Schweitzer to the effect that to be civilized men was practically the same thing as to remain human and humane beings, in spite of the environment created by modern so-called civilization. Only careful reflection on all the elements making up true humaneness could secure man from mistaking an external environmentally progressive civilization for civilization itself.

Professor Heringa reminded the Assembly that Article I of the Declaration of Geneva (the modern version of the Hippocratic oath adopted by the World Medical Association at Geneva in 1948) assumed that the medical practitioner had an absolute respect for human life. It was when he was confronted with suffering that the physician became most deeply aware of the sacerdotal side of his office. Article 6 in the Declaration of Geneva declared that the practitioner should never apply his science in violation of the laws of humanity. This implied, first of all, that in all his actions he should be led by his desire to decrease the suffering of his patient, and also that he should avoid everything that might increase the suffering or might undermine the physical resistance of the patient. The responsibility of a physician was no less when he involved a fellow man in his medical scientific work. Professor Heringa made it clear that the verdict whether certain medical procedures (diagnostic, therapeutic or scientific) were permissible or not did not belong to the realm of science or the technical skill of the physician but was comprised in medical ethics, which in itself was part of the human judgement between good and evil. Reference was made during the discussion to shocking and deplorable procedures that had been carried out by some combatants in the second World War. But it was not only to this kind of event that Professor Heringa referred. Both at the discussion itself and in private conversations before and after the session, it was clear that other matters had to be included—the planned therapeutic experiment in which certain patients were used as controls (perhaps to their detriment), and occasions when others were treated with a drug which was the subject of investigation, perhaps after animal experimentation had seemed to justify its use. This is made abundantly clear in the paper by Dr. William A. R. Thomson, Editor of *The Practitioner*, London, published in this issue. Dr. Thomson presented his paper after Professor Heringa had introduced the subject in his report. When we think of experiments carried out on human "volunteers", we must remember that persons volunteer for experiments for all kinds of reasons. Sometimes the volunteering may be the result of circumstances or of loyalties which are really in the nature of a compulsion. It has been suggested that the medical student, responding to the appeal of his medical teacher in the laboratory, or the technician in the laboratory who sees certain work carried out, may feel that he is bound to "volunteer" to be the human guinea-pig. It has also been suggested that experiments carried out in such organized bodies as the Air Force are almost compulsory for those who take part in them. Some of the participants in the discussion at Rome went so far as to assert that volunteering of this kind was not far removed from the experimentation which was reported as having taken place in totalitarian countries. Of course, the opinions about this will vary a

great deal, but whatever view is held it must be abundantly clear that the subject is far from simple and that it, at least, deserves careful consideration. Perhaps Dr. Thomson laid his finger on the most important point when he stated in regard to the acceptance of articles in medical journals that the integrity of the contributor was of the utmost importance. This is generally the person undertaking the experiment. Every medical community has its investigators who are widely known and respected and whose integrity would not be doubted for one moment. In a relatively small community like the medical profession of Australia these persons are known, but this may not be true of larger communities. There must be very few investigators who are not known and who wish to publicize their doings, right or wrong. A medical editor, or for that matter any investigator, can generally find out something about persons whose work seems peculiar and of whom he has never heard. There is little doubt that Professor Heringa is right when he declares that editors who fail in criticism or in caution in the matter of publication are as guilty as those who carry out reprehensible experiments. This is a sobering and wholesome thought. A further point was made by Professor Heringa when he stated that experience taught that a word spoken in public, and particularly when it is reported in the Press, acts far more suggestively than a pronouncement made at a private gathering. He declared that when true or would-be experts had once "made a breach in the ethical defence" the masses might lose the faculty of becoming indignant, and public opinion might become lost to all sense of the most primary ethical laws. *"Intellectual and cultured people are by no* means free from the characteristics attributed to the great masses and public opinion."

There is no doubt that every member of the community has to be particularly on his guard that he does not allow familiarity of ideas to breed contempt of action. This may require careful self-discipline, and this discipline must be unremitting. We may tell ourselves that every form of medical treatment is really an experiment, because treatment is not given to robots but to suffering human beings. And we know full well that no two persons react in the same way to any form of treatment. For all that, many practitioners still refer to persons who receive treatment at their hands as cases and not as patients. If we remember that the word patient comes from a Latin word meaning to suffer, we may not be so liable to fall into this elementary error. It may be held that this is a small matter and is really of no account, but it is really of the utmost importance. If we always refer to those who are ill as sufferers, we are not likely to do them as much harm as if we regard them as mere ciphers. In conclusion, it will be well to quote some words of Albert Schweitzer with which Professor Heringa concluded his report:[1]

> Intoxicated by the progress in discovery and invention with which our age has been flooded, we forgot to trouble ourselves about men's progress in spirituality. In the absence of all thought we slid without knowing it into pessimism, believing, that is, in all sorts of progress, but no longer in the spiritual progress of the individual and of mankind.
>
> Facts call us now to bethink ourselves, just as movements of their capsizing vessel drive the crew up on to the deck and into the rigging. Belief in the spiritual progress of the individual and of mankind has already become almost impossible for us, but with the courage of despair we must force ourselves into it. That we shall all unanimously again will this spiritual progress and again hope for it: that is the reversal of the helm which we must succeed in making, if our vessel is at the last moment to be brought once more before the wind.
>
> Only through thoughtful reverence for life shall we become capable of this achievement. If that reverence begins anywhere to work in our thinking and in our spirit and temper, then the miracle is possible. The power of the elementary and living spirituality that is to be found in it is beyond calculation.

[1] The translation by C. T. Campion is quoted in preference to that given by Professor Heringa.

Current Comment.

PLACEBOS.

THE question of the place of placebos in therapeutics has been once more raised by discussion on their inclusion in the National Formulary in Great Britain. In reply to a request for their inclusion, the Chairman of the Joint Formulary Committee, Professor E. J. Wayne,[1] states that the question has been frequently considered by the National Formulary Committee and most members would agree that there is a place for placebos in therapeutics. Nevertheless, there are considered to be serious objections to including such preparations in the Formulary, and the Committee decided against such a policy. Wayne suggests, however, that certain preparations, such as gentian and alkali mixture and *nux vomica* elixir, may be used as placebos in certain circumstances. Just what the objections are that the Committee has to including placebos in the Formulary is not stated. Certain it is that violently opposed views about placebos have appeared in the medical Press from time to time. Back in 1906, Richard C. Cabot,[2] in a strong attack on patent medicines, stigmatized the prescription of placebos as quackery. In particular, he objected to it because he regarded it as weakening the confidence of the patient in the physician, and also as fostering the habit of buying patent medicines. Much more recently, Thomas Findley,[3] Professor of Clinical Medicine in the Tulane University School of Medicine, has described the placebo as the most important therapeutic weapon which the physician has. Findley's view is that the placebo should not be used as an instrument of deception, but as "a technique for cementing the emotional bond which must attach doctor to patient if any form of treatment is to be really successful". He concludes (and the comment is serious rather than cynical): "For the vast majority of his patients it [the placebo] and himself are all that even the modern physician has to offer."

Both these statements are true from certain points of view, but neither gives the whole truth; nor does the in-between view that placebos are (in the words of R. P. Handfield Jones[4]) "unfortunate necessities". The fact about the placebo, anomalous as this may seem in the present age of specific therapy, is that recent work has been defining its place, in both clinical and experimental medicine, according to the best principles of rational scientific practice. Stewart Wolf,[5] as the result of deliberate pharmacological experiments with placebos, reached the conclusion that "placebo effects" which modify the pharmacological action of drugs or endow inert agents with potency are not imaginary, but may be associated with measurable changes at the end organs. Moreover, these effects are at times more potent than the pharmacological action customarily attributed to the agent. Wolf comments that the fact that placebo effects occur depends on the generalization established repeatedly by numerous workers that the mechanisms of the human body are capable of reacting, not only to direct chemical and physical stimula-

[1] *Brit. M. J. (Supplement), September 4, 1954.*
[2] J.A.M.A., September 29, 1906.
[3] *M. Clin. North America*, November, 1953.
[4] *Lancet*, October 17, 1953.
[5] *J. Clin. Investigation*, January, 1950.

tion, but also to symbolic stimuli, words and events which have somehow acquired special meaning for the individual. The frequency with which placebo effects are to be expected, and their magnitude, probably vary from person to person and from time to time. Wolf considers that not only the frequency but also the magnitude of placebo effects is impressive and deserves attention in pharmacological experimentation in animals and man. He points out that it is at present customary to control drug experiments on various clinical syndromes with placebos, especially when the data to be evaluated are chiefly subjective, but when objective recording of the indicators of the agent's effects are available, placebo control is not generally practised. The need for such controls is suggested by the fact that placebo effects include objective changes at the end organ which may exceed those attributable to potent pharmacological action. Indeed, pharmacological action of an agent may be outweighed and its effect thus reversed. More recently, Wolf and R. H. Pinsky[1] have reported the experimental use of placebos to test the effectiveness of mephenesin in the light of reports that this new drug exerted a specific effect on subjective anxiety and tension and on their objective manifestations. It was found that almost the same amount of improvement, or lack of it, occurred whether the patient was taking the mephenesin or the placebo. Moreover, toxic reactions were reported in both cases. Wolf and Pinsky quote the findings of a number of other investigators which parallel their own. For example, in investigations on the toxic effects of streptomycin, patients receiving only placebos have developed one or more of the evidences of streptomycin toxicity, including high-tone and low-tone hearing loss, eosinophilia and impairment of urea clearance. Other like results have occurred when placebos were used in the evaluation of vaccines and of vitamins in the prevention of colds.

A study of the placebo response by L. Lasagna *et alii*[2] focuses attention on the "placebo reactors". In this study, a group of 162 patients who had undergone operation was observed for the ability of the patients to receive significant relief of pain from subcutaneous injections of placebo and of morphine. The interesting point is not so much that a proportion of the patients obtained relief from a placebo (some consistently, some inconsistently) and that another group consistently failed to react, but that there was a significantly higher incidence of relief from morphine in the "placebo reactors" than in the non-reactors. In other words, in the "placebo reactor" there is not only a simulation of the effect of the drug being tested when only a placebo is given, but also a reinforcement of the action of the drug when the drug itself is given.

This concept of the placebo reactor has important implications. As Lasagna and his colleagues point out, an impairment of ability to discriminate between active drugs and inert substances is implicit in the phrase "the placebo reactor". It is obvious that a population composed exclusively of such individuals would be unsatisfactory for the evaluation of certain kinds of drugs, and investigators concerned with the evaluation of drug effects should be aware of the fallacies involved. The idea of using a placebo is to provide a very necessary control in the assessment of the action of a drug in a therapeutic trial. On the other hand, as is pointed out in this article, the placebo effect can be one reason for failure to recognize a useful drug in such a trial. Lasagna and his colleagues discuss various ways in which the placebo response can be taken into account in therapeutic trials, but there are many difficulties; nor is it easy to pick out the reactor type, despite the confidence of many physicians and nurses in their ability to do so. Data collected by Lasagna and his colleagues from the Rorschach test and from interviews indicate that consistent reactors and non-reactors possess certain different psychological characteristics. Thus, the reactor is, in their view, a recognizable type, but only in the sense that intensive interview and psychological testing can differentiate him from a non-reactor. Off-the-cuff impressions by interviewers about which patients were reactors were more often wrong than right. For example, the reactors were not whiners or nuisances, they were not typically male or female, young or old, and they had the same average intelligence as the non-reactors. The reported data suggest that, should it be desirable to exclude consistent reactors from the study, this might be accomplished in advance by excluding those patients who showed a preponderance of the Rorschach signs noted. These signs cannot necessarily be expected to identify the occasional reactor. Lasagna and his colleagues discuss the underlying factors in the placebo response at some length and reach the following working hypothesis, which they regard as reasonable. They suggest that there is a certain psychological set which predisposes to anticipation of pain relief and thus to a positive placebo response. The presence of the traits making this set is probably not an all-or-none phenomenon, but rather a graded one. Other factors, such as severity of pain, also affect the response to inert agents, and the resultant of these factors, psychological and non-psychological, known and unknown, determines whether or not a particular dose of placebo produces an effect in a given patient.

This important work is more particularly relevant to large-scale therapeutic trials of new drugs, and demands the careful attention of all who are concerned with such trials. However, it is also interesting to the clinician, either when he is using a new drug or when he deliberately prescribes a placebo for a patient. He may not be able to identify the placebo reactor, who is, it would appear, an elusive identity, but he should have it in mind that an apparently inert placebo can produce a measurable physiological response and that the response of a placebo reactor to a potent drug can be different from, and indeed greater than, that of a non-reactor. Whether or not clinicians should prescribe placebos at all in their normal practice is another matter altogether. The pros and cons have been thoroughly discussed recently in two articles from England[1] by A. Barham Carter and by R. P. C. Handfield Jones and in an American article by Alan Leslie.[2] This last-mentioned article contains an interesting discussion of the ethics of the matter, propounding a fine line of distinction between the words "deception" and "deceit", and then goes on to consider the indications for placebos and the technique of their prescription and use in considerable detail. The English articles are rather more down to earth, but in general they present the same ideas. The consensus of opinion is that there is a place for placebos in medical practice. Some think it greater than others, but all agree that it is only an adjunct to sound deliberate medical management founded on careful investigation and diagnosis. The misuse of placebos well merits Cabot's strictures. It is quackery, no matter who practises it.

[1] *J.A.M.A.*, May 22, 1954.
[2] *Am. J. Med.*, June, 1954.

PHYSICAL ACTIVITY AND RECOVERY FROM *HEPATITIS.*

VIRAL HEPATITIS has claimed a great deal of attention in recent years, especially since it has been realized that chronic hepatitis is a not uncommon sequel. As a result, increasing care has been shown in the long-term after-care of patients, and the period of active treatment has often been much prolonged. Recent reports suggest that it may have been too much prolonged. The period of loss of time amongst certain groups of men in the United States Armed Forces in Europe is stated to have increased from as little as thirty days in 1942 to as much as ninety days in 1951. This constituted a major military problem and so stimulated efforts to determine whether a modified regime of rest might be effective. Earlier reports indicated that this was so, and a recent follow-up study by R. S. Nelson *et alii*[3] has confirmed the finding. The follow-up study covered 80 patients, presumably recovered from viral hepatitis, who were reexamined twenty-two to thirty-three months later. The treatment routine generally employed in

[1] *Lancet*, October 17, 1953.
[2] *Am. J. Med.*, June, 1954.
[3] *Am. J. Med.*, June, 1954.

Germany at the time when these men were suffering from viral hepatitis is briefly stated. Efforts were made to keep patients in bed (with the privilege of going to the bathroom) for at least three weeks after the onset of symptoms or until they were asymptomatic without hepatic tenderness and until the one minute direct serum bilirubin value measured less than one milligramme per 100 millilitres. At this point in convalescence they were allowed out of bed with the privilege of walking to the mess hall, theatre or recreation rooms. When the excretion of intravenously administered bromsulphthalein was normal, and if the patients were asymptomatic, they were given a test of tolerance of exercise for five days. If, at the end of that time, the excretion of bromsulphthalein remained normal and there was no clinical evidence of relapse, the patients were discharged to duty. In practice, many of the men indulged in a great deal more activity than that prescribed, even when they were still suffering from a considerable degree of jaundice and other indications of altered hepatic function.

The 80 patients considered in this study were all still in Germany at the time of the examination. The only criterion for their selection for the study was their availability. It was found that all had been able to do full duty and, with the exception of intercurrent infections, had apparently enjoyed good health. All but five admitted drinking some alcoholic beverage daily, and 18 of them consumed large amounts regularly. All but two were in apparently good physical condition; the two exceptions were regarded as being poorly developed and undernourished. In response to questions and physical and laboratory examinations more specifically related to hepatic disease, 46 of the 80 men had complaints, physical signs or mild abnormalities of hepatic function, singly or in combination, which might serve to call attention to the possibility of disease of the liver; but none of the 40 patients in whom biopsy was performed had any histological evidence of incipient or fully developed cirrhosis, of chronic progressive hepatitis or even of significant scarring of the liver. In some cases, minor abnormalities were seen in the biopsy specimens; but, according to Nelson and his colleagues, it is impossible in the present state of knowledge to attribute these findings unequivocally to the attack of hepatitis which these patients had had two to three years previously, and actually the degree of alteration seen was so mild as to be of no particular significance in their experience. It is noted that the simultaneous occurrence of symptoms, signs and abnormal results from tests of hepatic function was rare, and only four of the 80 patients had defects in all three categories. In addition, there was little relationship between the presence of symptoms or signs and abnormal results from tests of hepatic function. Nelson and his colleagues make the comment that the lack of correlation between the occurrence of complaints and objective findings, as well as their mild character, makes it impossible to interpret the significance of the fact that as many as 46 of the 80 men in question had deflections from normal at the time of reexamination. They suggest a number of possible reasons for this disparity, but while unable to decide which one or which combination of these possibilities is true, state that it is quite apparent that there was insufficient evidence in any case to justify the diagnosis of chronic hepatitis.

The general conclusion drawn from the data presented in this study is that they support previous observations in Germany that activity in excess of that usually prescribed in the treatment of patients suffering from viral hepatitis apparently need not prolong the course of the disease or inhibit sustained recovery. In addition, there was nothing to suggest that excessive indulgence in alcohol, intercurrent infections or recurrence of jaundice during the period of approximately two to three years after recovery had any untoward effect. These findings are said to be further supported by the results of recent carefully controlled studies from the hepatitis centre of the United States Armed Forces in Japan, where it has been shown that allowing men out of bed for most of the time from the first day of admission to hospital for hepatitis did not prolong the course of disease. It is pointed out that a less conservative regime of therapy for young adults with viral hepatitis is not associated with any apparent ill effects, and is in accord with the experience in treatment of the disease in children, to whom less stringent rules of therapy have usually been applied.

One point that is not clear from this study is that the men examined were really a representative selection of those who were originally treated. All were still on duty in Germany, and, as already stated, the only criterion for selection of patients for reexamination was their availability. It would be of interest to know if the non-availability that excluded men from selection was due in any case to their having died or having been invalided home from Germany for conditions that might or might not be related to their attack of viral hepatitis. Thus, while the data published may be said, quite reasonably, to justify the conclusions drawn in relation to the 80 men studied, they do not, as they stand, allow for generalizations.

THE SURGICAL ASPECTS OF BULLFIGHTING.

MOST thinking people in this country regard the idea of bullfighting with, at least, distaste, and find little to differentiate it from such outlawed pastimes as cockfighting, bear-baiting and even gladiatorial combat. Whether they will be converted from this view by the enthusiasm of Willem P. Steenkamp, junior,[1] is another matter, but there is a great deal of interest in what he has to say about the surgical aspects of this popular Spanish custom. Steenkamp describes bullfighting, or rather bull-running (*corrida de toros*), as a highly scientific as well as a polished sport, demanding an intricate knowledge of animal psychology and anatomy, as well as nerves of steel and intense physical fitness on the part of the *matador* and his team. According to Steenkamp's account, the bullfight takes half an hour; this is subdivided into different periods, and each period is announced by a fanfare of trumpets. The bull meets, first, the *toreros* or runners, who are unarmed, and then the *picadors* or mounted pikemen, who tire and infuriate the bull with their lances and short barbed javelins. Finally, the *matador*, alone in the arena with the bull, is allowed ten minutes to complete the kill. His aim, according to the rules of the game, is to sink his sword directly into the mediastinum at a recognized spot between the tips of the bull's scapulæ, to puncture either the heart or the aorta and so cause instant death. This act is the culmination of ten minutes' activity of the highest skill and danger. One mistake may well cost the *matador* his life.

The type of injury inflicted on the *matador*, according to Steenkamp, usually depends on the stage of the fight. While "playing" the bull, the *matador* frequently receives glancing blows from the horns, but his tightly fitting silk costume offers very good protection against this contingency. Failure in the act of killing the bull may mean the bull throws up his head violently, catching the *matador* in the groin, penetrating the abdomen or tossing him to the ground. A well-equipped operating theatre with all modern facilities and a ward are attached to all arenas. Despite the very real danger to the *matador*, the number actually killed is very small, and figures quoted indicate that major injuries are surprisingly few. Steenkamp says that the highest mortality seems to be among the *espontaneos*, the youngsters who slip through the cordon of police and jump into the arena, often armed only with a stick and overcoat. They play the bull until they are dragged out of the arena and sent to gaol for ten days. Their motive is to catch the eye of some prospective patron who might finance their training. The rarity of serious or fatal injuries to a *matador* is attributed to the fact that the recipient is on the move when the injury is sustained, and thus the horns glance off the tight-fitting silk uniform. Moreover, the *matador's* abdomen is swathed in several layers of linen, and his ankles are strapped to prevent twisting or spraining. The average *matador* starts at the

[1] *South African M. J.*, September 11, 1954.

age of eighteen years, but usually retires early, for after about seven years he is said to have made enough money to buy a ranch and breed bulls.

From Steenkamp's description, bullfighting must be, in many respects, a brilliant performance, but he will not convince everyone with his *apologia* for certain essential features that are usually criticized. It is doubtful whether the figures he quotes to show that bullfighting causes fewer casualties than rugby would stand up to any sort of critical examination. It is admittedly easy to sentimentalize about the bull, which is bred for ferocity and readiness to undertake battle; but it is no sort of argument to say that the sport is less cruel than starving and overcrowding in trucks, or inhumane methods of killing in abattoirs. Apart from this, Steenkamp says nothing about what this bloody spectacle, centred in killing, does to the onlookers.

THE EFFECTS OF CORTISONE AND CORTICOTROPHIN ON THE HUMAN ADRENAL CORTEX.

IT has been known for a good long time that, in animals, atrophy of the adrenal cortex follows the administration of cortisone, and that hypertrophy follows the administration of corticotrophin (ACTH). Clinical observations suggest similar changes in man, but comparatively little direct evidence has been published about this, and in particular, little attention has been paid to histochemical changes in the adrenal cortex. Attention has been recently drawn to these histochemical changes by H. B. Stoner and H. J. Whiteley,[1] and in view of the increasing use of cortisone and corticotrophin in clinical practice, the implications of these changes should be more widely appreciated. Stoner and Whiteley's conclusions are based on five cases previously reported and on seven examined in the present paper. A detailed account is given of the histochemical findings, but they may be summed up by stating that after treatment with corticotrophin there were found signs of hypertrophy and increased activity, and after treatment with cortisone acetate there were found signs of inactivity and atrophy. Stoner and Whiteley state that the cause of death of patients under treatment with corticotrophin could easily be related to the condition for which the hormone had been given, but this relationship was not so clear in the patients who had died while under treatment with cortisone. They hasten to point out that many patients have been successfully treated with both forms of therapy; nevertheless, they feel that the different effects of these hormones on the gland should have some influence on the choice of therapy when factors such as hypersensitivity do not play a part. The end result of a course of corticotrophin therapy is an enlarged and active adrenal gland, whereas after a course of cortisone therapy the gland is atrophic and inactive. The assumption made that the atrophic gland will revert to normal after the cessation of treatment is largely based on the behaviour of the rat, a species which, it is pointed out, is not subject to Addison's disease, and in which cortical regeneration is very rapid after such violent procedures as adrenal enucleation. In many human cases, cortical regeneration is thought to have taken place after cortisone therapy, but Stoner and Whiteley wonder whether it always takes place or whether a point of atrophy can be reached beyond which there is no return.

These findings, combined with those of other workers, illustrate the damage which can be produced by therapeutic doses of cortisone. It seems likely that a situation can be created by the use of cortisone which will greatly impair the efficiency of the body in dealing with any further assault. For these reasons, Stoner and Whiteley suggest that the use of corticotrophin is preferable to that of cortisone in cases in which an excess of circulating cortical steroid is required, unless, of course, there is some over-riding contraindication to the use of corticotrophin, such as hypersensitivity to the hormone. This suggestion is of special importance in cases in which surgical intervention at a later date is contemplated.

[1] *Lancet*, November 13, 1954.

CORNEAL GRAFTING IN SOUTH AUSTRALIA AND VICTORIA.

ON October 21, 1954, assent was given to an amendment of *The Anatomy Act*, 1884-1934, of South Australia. The amendment is known as the *Anatomy Act Amendment Act*, 1954. The object of the amendment is to provide for the removal of the eyes of deceased persons for the purpose of corneal grafting. The chief clause of this Act is as follows:

> 18a. (1) If any person, either in writing at any time or orally in the presence of two or more witnesses during his last illness, has expressed a request that his eyes be used for therapeutic purposes after his death, the person lawfully in possession of his body after his death may, unless he has reason to believe that the request was subsequently withdrawn, authorize the removal of the eyes from the body for use for those purposes.

The second clause states that without prejudice to the clause already quoted, the person lawfully in possession of the body of the deceased person may authorize the removal of the eyes from the body for the purposes mentioned, unless that person has reason to believe, first, that the deceased person had expressed an objection to his eyes being so dealt with after his death and had not withdrawn it, or secondly, that the surviving spouse or any surviving relative of the deceased person objects to the eyes of the deceased person being so dealt with. Another clause states that no removal of an eye shall be effected except by a legally qualified medical practitioner, who must have satisfied himself by personal examination of the body that life is extinct. No authority may be given for the removal of an eye if it is likely that an inquest will be held on the body, and in this case, consent of the city coroner is required. Another clause provides that in the case of a body lying in a hospital, any authority under the section may be given (*a*) by the person having control and management of the hospital; or (*b*) by any person authorized in writing by the person having such control and management. The Act is to come into force three months after it has been passed.

Victoria has made a similar kind of provision and has passed the *Corneal Grafting Act*, 1954. The principal clause states that where a person has during his lifetime by writing in the prescribed form or to the like effect directed that his eyes be used for therapeutic purposes after his death, that direction shall be sufficient authority for the removal of the eyes from his body after his death and their use for the said purpose. No such removal shall be effected except by a legally qualified medical practitioner who first satisfies himself by personal examination of the body that life is extinct. The Act has a provision about coronial inquiries similar to that of South Australia.

THE TRANSACTIONS OF THE ROYAL SOCIETY OF SOUTH AUSTRALIA, INCORPORATED.

WE have received a copy of the centenary volume of the "Transactions of the Royal Society of South Australia, Incorporated". In addition to an account of the centenary meeting of the Society, which was held on September 24, 1953, this volume contains a series of scientific articles (botanical, zoological, geological, anthropological) all relating to the Australian scene. The Society is desirous of extending its list of exchanges of scientific publications, and draws attention to back sets of its publication which are available for exchange with scientific bodies interested in the same general spheres of research. Further inquiries or orders for sets should be addressed to the honorary treasurer, Royal Society of South Australia, 2 Kintore Avenue, Adelaide, South Australia.

Abstracts from Medical Literature.

PHYSIOLOGY.

Combined Effect of Alcohol and Hypoxia on Flicker Fusion Frequency.

R. ROKSETH AND F. V. LORENTZEN (*J. Appl. Physiol.*, March, 1954) report that on the assumption that moderate lack of oxygen might increase the effect of alcohol in man, experiments were carried out on 25 healthy subjects, aged twenty to twenty-five years, to measure the deviation in flicker fusion frequency brought about by a combination of alcohol and hypoxia. Alcohol, given in doses of 0·5 to 0·7 gramme per kilogram of body weight, when combined with a simulated altitude of ten thousand feet, caused in most subjects a greater decrease in flicker fusion frequency than alcohol or hypoxia alone. When the results were related to blood alcohol level, a decreased performance was present at concentrations of 0·03% to 0·04% after two to four hours' hypoxia. The authors state that there seems to be a simple addition of effects. They discuss the physiological and practical implications—for example, for airmen.

Respiratory and Circulatory Effects of Mechanical Respiration.

H. L. PRICE, E. H. CONNER AND R. D. DRIPPS (*J. Appl. Physiol.*, March, 1954) report a comparative study of the effects of several mechanical respirators on pulmonary ventilation and systemic arterial pressure in anæsthetized human subjects. All the respirators studied were capable of ventilating the average apnœic subject adequately, but in obese individuals the "Pneolator" occasionally did not produce a sufficient tidal volume when operated in the same mask pressure range as was employed with the other respirators. At any given level of mean mask pressure the intermittent positive-pressure devices (Bennett and M.S.A. experimental model) and the positive-negative pressure devices produced approximately equal tidal and minute volumes of ventilation, but the cyclic positive pressure machine studied ("Pneolator") produced less than either of the other two types. Some subjects who had slight ability to respire apparently tolerated the intermittent positive pressure devices and the cyclic positive pressure valve better than the positive-negative pressure machines. Adequate ventilation could be produced without a decrease in arterial pressure by any of the devices studied in subjects who showed "moderate" vasomotor reactivity. In subjects whose vasomotor reactivity had been greatly reduced by the administration of spinal anæsthesia, ganglionic blocking agents or large amounts of sodium thiopental, the level of arterial pressure decreased during mechanical ventilation of the lungs at all pressures greater than atmospheric, and the amount of this decrease was related both to the prevailing level of mean mask pressure and to the time the respirator remained in operation. Apnœic individuals with greatly reduced vasomotor reactivity who were ventilated at mean mask pressures less than atmospheric usually showed an increase in arterial pressure during this procedure.

Effect of Barbiturates on Patients with Liver Disease.

J. T. SESSIONS, JUNIOR, H. P. MINKEL, J. C. MULLARD AND F. J. INGELFINGER (*J. Clin. Investigation*, August, 1954) report that pentobarbital in hypnotic doses was given to patients with severe liver disease and to control subjects. The effects of the drug were studied by clinical observations, liver function tests and measurement of barbiturate blood levels. No evidence was obtained that patients with liver disease were more sensitive to single injections of pentobarbital, or that the early removal of the drug from the blood of these patients was delayed. Prolonged administration of pentobarbital to patients with decompensated liver disease did not appear to retard recovery in 12 of 13 trials. The authors state that the use of sedatives in patients verging on hepatic coma is not recommended, but the specific dangers ascribed to barbiturates in patients with liver disease appear to have been overemphasized.

Some Postural Adjustments of Salt and Water Excretion.

M. L. PEARCE, E. V. NEWMAN AND M. R. BIRMINGHAM (*J. Clin. Investigation*, August, 1954) report that with the normal human subject undergoing moderate water diuresis, quiet standing results in a slight depression of creatinine clearance and a marked depression of sodium, chloride, potassium and water excretion as compared with control measurements with the subject in the supine position. If the legs are wrapped with elastic bandages before the orthostatic position is assumed, the depression of salt excretion is inhibited with varying effect on the antidiuresis. On the other hand, administration of alcohol inhibits the orthostatic antidiuresis and enhances the orthostatic inhibition of salt excretion. It is suggested that there are separate postural adjustments of water and salt excretion, the former under diencephalic posterior pituitary control and the latter under the control of some mechanism sensitive to the distribution of interstitial fluid.

Thermal Responses of Men with High Initial Temperatures to Stress of Heat and Work.

C. H. WYNDHAM, N. B. STRYDOM, J. F. MORRISON, F. D. DE TOIT AND J. G. KRAAN (*J. Appl. Physiol.*, May, 1954) state that out of 463 African labourers investigated in their laboratory between February and August, 1952, 37 (or 7·9%) were found to have mild medical complaints and body temperatures which were above average at the beginning of the experiments. While under close medical supervision, most of these men were subjected to the stress of exercise in cool or hot humid conditions. This was done because, as far as is known, no such study exists, and it is of great practical importance to industry to know what happens to similar men when they are required to do manual work. From the information obtained it was decided to investigate a possible relationship between initial body temperature and the highest achieved during work under the various conditions of heat stress studied. The authors further report that these new recruits with symptoms of mild illness and rectal temperatures above 100° F. readily attain rectal temperatures of 104° F. in conditions of moderate and severe heat stress. At such rectal temperatures most men were distressed. On the level of initial resting rectal temperature, it is possible to predict which men will develop the highest rectal temperatures during work in hot conditions.

The Mechanism of Transportation of the Content of the Œsophagus.

KAGO HWANG (*J. Appl. Physiol.*, June, 1954) reports that the present knowledge regarding œsophageal function has been critically reviewed and the mechanism of the transportation of the content in the œsophagus has been further investigated in the dog. Secondary peristalsis is present throughout the entire length of the œsophagus, and the threshold for its initiation is higher in the cervical than in the thoracic portion. There is probably a common set of efferent fibres for both the primary and the secondary peristalsis of the œsophagus. Afferent fibres for the secondary peristalsis of the thoracic portion of the œsophagus are present in the vagus nerves together with the motor fibres. Specific afferent fibres for the secondary peristalsis of the cervical portion of the œsophagus may be found in the communicating branch between the inferior and superior laryngeal nerves. The secondary peristalsis of the œsophagus, like the primary, is under central control. Successive peripheral stimulations causing a chain of reflexes are normally present but are not necessary for its maintenance. Secondary peristaltic activity of the upper segment of the œsophagus was found to have an inhibitory effect on the similar activity of the lower segment. This inhibitory effect of the activity of the upper part on the lower part from the pharynx to the cardia and fundus of the stomach may be the most important central mechanism of the polarity and efficiency of œsophageal peristalsis. The primary peristalsis of the œsophagus is apparently not different from the secondary peristalsis in relation to the speed of progress, the force of propulsion and the ability to jump over a gap. In the normal physiological process of deglutition both the secondary and primary peristalsis play an important role.

BIOCHEMISTRY.

Testosterone.

H. H. WOTIZ AND H. M. LEMON (*J. Biol. Chem.*, February, 1954) have shown that benign hypertrophic human prostate metabolizes testosterone; Δ^{+}-androstenedione-3,17 was identified as one of the metabolites.

Acetaldehyde.

J. F. BERRY AND E. STOLZ (*J. Biol. Chem.*, June, 1954) have studied rat brain homogenates and shown that acetaldehyde

increased the synthesis of acetylcholine and acetoin and decreased the formation of citric acid from pyruvate or acetate. Acetaldehyde was observed to support some acetylcholine and citric acid synthesis when used as the sole acetyl donor. Alcohol had no effect on acetoin or citrate synthesis, but increased acetylcholine formation.

Albumin.

F. ULRICH *et alii* (*J. Biol. Chem.*, July, 1954) have studied the effect of prolonged administration of growth hormone, ACTH and thyroxine on the metabolism of plasma albumin in adult hypophysectomized rats with S^{35}-labelled albumin. In the hypophysectomized rat the initial effect is a decrease in the rate of albumin synthesis. The replacement rate in the normal rat is about twice as high as in the hypophysectomized animal. Treatment of the hypophysectomized animal with growth hormone results in a great stimulation of albumin synthesis, so that the replacement rate is increased twofold or more. Thyroxine does not potentiate the effect of growth hormone. Treatment of the hypophysectomized animal with ACTH results in an initial increase in the rate of albumin degradation, together with an insignificant effect in the direction of increased replacement rate. Growth hormone and ACTH, administered to the hypophysectomized animal, have antagonistic effects. Under the conditions of these experiments the replacement rate was increased by a combination of the two.

Cholesterol.

E. WAINFAW *et alii* (*J. Biol. Chem.*, April, 1954) have shown that incubation *in vitro* of fæces or intestinal contents of cholesterol-fed rats results in a significant decrease in total cholesterol content. A number of microorganisms which can utilize cholesterol were isolated in pure culture from the fæces of cholesterol-fed rats. Two of the species most active in this respect were identified as *Aerobacter aerogenes* and *Pseudomonas jaegeri*.

Absorption.

T. H. WILSON (*Biochem. J.*, March, 1954) has shown that when glucose-containing saline was circulated through rat intestine the concentration of lactate rose on the serosal side up to nine times that on the mucosal side within one hour. The bicarbonate concentration decreased to about one-half the original value on the mucosal side, while that on the serosal side remained practically constant. Thus glucose is converted into lactic acid, the lactate appearing mainly on the serosal side, the hydrogen ion appearing on the mucosal side. This was confirmed in experiments with sacs of everted intestine of the rat. Concentration gradients of lactate of six to 20 were observed. The concentration of bicarbonate decreased on the mucosal side, while that on the serosal side remained constant or increased. Anaerobically the bicarbonate concentrations on both sides of the sacs of rat intestine decreased, the decrease being equivalent to the increase in lactate concentration on the two sides. The lactate gradient did not disappear under anaerobic conditions. It is suggested that the conversion of glucose into lactate may play a role in the absorption of glucose *in vivo*. Sacs of everted ileum from the hamster can transfer bicarbonate from serosal to mucosal sides against a concentration gradient.

Plasma Protein.

H. L. STEINBOCK AND H. FARRER (*J. Biol. Chem.*, July, 1954) report that the percentage of protein in the diet greatly influences the half-life and the rate of replacement of the plasma protein in rats. With a protein-free diet the replacement rate is small, whereas with a high protein diet it may be two or more times as high. From changes in half-life, replacement rate and pool size, which occur when the protein content of the diet is changed, it is deduced that such changes may cause an increase either in rate of synthesis or in rate of degradation, depending on the nature of the original diet.

Progesterone.

N. C. SLEN *et alii* (*J. Biol. Chem.*, May, 1954) have reported that after intragastric administration of progesterone-21-C^{14} to normal rats, approximately 15% of the administered radioactive material was eliminated in the expired air, 30% in the urine and 55% in the fæces. In animals with cannulated bile ducts, the bile served as the major route of excretion, while in animals with ligated bile ducts, the kidney assumed this function. Metabolites of progesterone were excreted more rapidly after intragastric than after intramuscular administration, which might explain, in part, the relative inactivity of orally administered progesterone. The appearance of C^{14} in the expired air and in urinary urea indicates that oxidative scission of the side chain of progesterone-21-C^{14} occurred, with subsequent fixation of carbon dioxide.

Pyridoxin.

J. R. BEATON *et alii* (*J. Biol. Chem.*, March, 1954) have investigated the time of onset of biochemical defects in the vitamin B_6-deprived rat. Differences in carcass levels of total crude fatty acids and tissue levels of total vitamin B_6 were evident within one week of deprivation. Significant alterations in nitrogen metabolism were not evident until after at least four weeks, when body weight, carcass level of total crude fatty acids and tissue levels of total vitamin B_6 had attained constant values. Activity of liver transaminase of vitamin B_6-deprived rats did not decrease, but failed to increase with time, as in control animals. The results of this study indicate that disturbances in nitrogen metabolism in the vitamin B_6-deficient rat may be secondary to a primary effect on energy production which deprives the animal of surplus food for storage as fat.

Vitamin B_{12}.

W. R. PITNEY *et alii* (*J. Biol. Chem.*, March, 1954) have studied the binding of vitamin B_{12} by normal serum in two ways: (*a*) the total binding capacity following the addition of excess crystalline vitamin B_{12} has been determined, and (*b*) the location of the bound vitamin in serum has been investigated by an electrophoretic technique. Normal serum has a limited capacity to bind added crystalline vitamin B_{12} *in vitro*. Upon the addition of 1000 micromicrogrammes of crystalline vitamin B_{12} to one millilitre of serum, the mean concentration of bound vitamin increased from 178 to 336 micromicrogrammes per millilitre. The binding of vitamin B_{12} by serum protein is a specific phenomenon for which the α-globulin fractions are responsible. Serum albumin does not play a part in the transport of vitamin B_{12} in the circulation. The other globulin fractions, likewise, have little activity in this respect. When crystalline vitamin B_{12} is added to serum *in vitro*, the major part of the added vitamin which is bound can be recovered from the α-globulin fractions.

Hydroxykynurenine.

C. E. DALGLIESH AND S. FEKMAN (*Biochem. J.*, March, 1954) have found that in a large proportion of cases the febrile human excretes hydroxykynurenine. This excretion is, in particular, unrelated to tuberculosis or diabetes. It is attributed to a high rate of breakdown of body protein. In states associated with weight loss but not accompanied by fever, hydroxykynurenine excretion could not be detected. The normal human taking an excess of tryptophane by mouth excretes much kynurenine, but no hydroxykynurenine (or negligible amounts).

Uric Acid.

D. WILSON *et alii* (*J. Biol. Chem.*, July, 1954) have studied uric acid excretion after ingestion of nucleic acid. Two normal young male subjects and one elderly male with non-tophaceous gout each ingested about one gramme of yeast nucleic acid labelled with N^{15} in both the purine and pyrimidine moieties. The slopes of curves for the excretion of isotopic urinary uric acid were very similar to the uric acid "turnover rates", which were determined separately after the intravenous injection of isotopic uric acid. On the basis of this and the amount of purine nitrogen excreted as uric acid, it was concluded that the purines of the ingested nucleic acid were rapidly converted to uric acid, or possibly to some unknown precursor whose "turnover rate" was very similar to that of uric acid. Normal and gouty subjects did not seem to differ significantly in their ability to do this.

Iodine.

D. M. FAWCETT AND S. KIRKWOOD (*J. Biol. Chem.*, July, 1954) have described an enzyme which catalyses the reaction between elemental iodine and tyrosine to produce mono - iodotyrosine. The occurrence of this enzyme in the submaxillary salivary gland, when considered with other evidence, indicates that this organ may be involved in the extrathyroidal metabolism of the hormone thyroxine. The reaction of tyrosine iodinase may be coupled with chemical reducing agents. The addition of cysteine to actively synthesizing preparations will cause the action to be reversed.

Special Articles for the Clinician.

(CONTRIBUTED BY REQUEST.)

CXI.

SOME HAZARDS IN FRACTURE TREATMENT.

THIS short paper has been written in the hope that it may be of some assistance to those general practitioners who undertake the treatment of a certain number of fractures.

In the last quarter of a century methods of reducing fractures and maintaining reduction have gained a great deal in precision. More mechanization has been introduced into fracture treatment, and the materials used for internal fixation of fractured bones have been improved greatly.

The increased availability of blood transfusion and the remarkable advances in chemotherapy have made open reduction and fixation of fractures a much safer procedure than it ever was before.

The whole subject of traumatic surgery is passing through a stage of seething activity, and methods are changing so rapidly that it is hard to keep pace with them. In the midst of this exceedingly active period it should be a salutary exercise to ponder over some of the current methods and to try to take a dispassionate view of their advantages and disadvantages. Many of the methods have not been in use sufficiently long for an accurate assessment of their value to be made.

This paper is not intended as an exhaustive survey of results, but more as a recording of clinical impressions and perhaps as a stimulus to further thought and discussion in a difficult and important subject.

Plaster of Paris Casts.

Plaster casts as a method of fixation of reduced fractures have increasingly come into vogue instead of metal splints. They have the advantage that they can be made to fit the shape of the affected limb accurately.

Before Lorenz Böhler wrote his excellent book on fractures the fractured limb was usually padded before the plaster cast was applied. He strongly advocated the use of non-padded casts, and another authority, Sir Reginald Watson-Jones, also endorsed this method in his book on fractures.

Largely as a result of the teaching of these two authorities the use of non-padded casts has become very prevalent. There is no doubt whatever that the non-padded plaster cast holds the fragments of a fractured long bone more effectively than a padded cast. The non-padded cast, however, has certain serious disadvantages.

It constitutes a rigid casing around the limb and leaves no room for expansion. It can, therefore, be a potential cause of ischæmia of the limb unless it is used judiciously by doctors with considerable experience of traumatic surgery. As a general principle I would suggest that if there is a likelihood of a limb swelling inside the cast a non-padded cast should not be used.

A small amount of padding can be applied to the anterior surface of the leg and dorsum of the foot or to the anterior surface of the forearm and to the palm of the hand in the form of a long band or strip of cotton wool moulded smoothly into the limb. This greatly diminishes the risk of ischæmia without interfering greatly with the retentive action of the cast. As an additional precaution the cast may be applied over a strip of motor tire tube rubber placed longitudinally. When the plaster is almost set, the surgeon cuts through the cast down on to the rubber, thus avoiding cutting the skin. The rubber strip is now removed. The surgeon now has command of the situation.

In the event of the development of a threat to the circulation in the limb the two sides of the split cast may be spread further apart until the circulation in the fingers or toes becomes satisfactory. When the swelling of the limb has settled down, it is usually advisable to change the cast, as it otherwise becomes loose. A non-padded cast can now be applied, and this greatly diminishes the risk of loss of position of the fragments. The risk of ischæmia is greatly decreased if all patients with plaster casts applied for fracture are admitted to hospital for the night. The hospital staff are instructed to watch the circulation and sensation frequently and to have the patient examined by a doctor if there is any serious interference with them. Instructions are also given that if any delay is likely the nursing staff may spread the split cast apart far enough to relieve the circulation.

Injections of morphine for pain are used only with great caution while the circulation is bad. Often the pain is due to a threat of early ischæmia and the morphine, by masking the pain, is likely to discourage the nursing staff from spreading the cast or getting expert help.

In out-patient hospital treatment of fractures it is common practice for the surgeon to apply a non-padded cast to the injured limb and to send the patient home with a bottle of sedative mixture. This is a hazardous practice, especially in a patient who has a good resistance to pain and who will perhaps not report back to hospital even when pain is severe.

With or without careful precautions the doctor may at times be suddenly faced with a cold, pulseless limb in the course of treatment of a fracture or even before treatment has commenced. Perhaps the fractures which are most commonly associated with this condition are supracondylar fracture of the humerus in children and the femoral supracondylar fracture in adults. The condylar fragment of the humerus is displaced backward, and the brachial vessels are liable to be bent sharply where they impinge on the sharp anterior edge of the upper fragment. This causes obstruction to the circulation. In addition, spasm of the brachial artery may occur, resulting in great diminution in the calibre of this vessel. Something must be done urgently. A kind of superstition exists among some medical men that the great swelling which is present is a contraindication to reduction of the fracture. On the contrary, the first surgical step to be taken should be the reduction of the fracture under general anæsthesia. This removes the pressure on the vessels and releases the kink. No other measure may be necessary to relieve the ischæmia, although the radial pulse may take hours to return. Provided that the fingers are warm and pain is not severe, the absence of the radial pulse should not be regarded as an indication for open operation. If, however, evidence of severe ischæmia persists, section of the deep fascia overlying the ischæmic muscles with exposure of the brachial vessels is indicated. If the brachial artery shows diminution of its calibre due to spasm, local application to the artery of a 2·5% solution of papaverine sulphate should be tried. I do not know from experience the effect of this measure or of any operative procedure on the vessel.

The brilliant observations of Kinmonth (1952) suggest that this local application constitutes the most effective means of causing relaxation of arterial spasm.

The Use of Weight Extension.

The value of traction on a fractured limb, both as a means of achieving reduction and as an excellent retaining factor, is undeniable.

It is interesting to note that many good results in fracture of the femur have been and are still being obtained by the use of adhesive plaster traction on a Thomas's splint. With the powerful muscles of strong adults to deal with, the chances of obtaining full length and perfect reduction by this method are not as great as in children, for whom, in my opinion, adhesive plaster traction should still be the method of choice. In adults this technique has largely been replaced by skeletal traction.

The Steinmann pin had a large vogue, but in using this the pin has to be hammered through the bone; this is a rather traumatic process. The method lost some of its popularity when cases of osteomyelitis occurred, but many still prefer to use it. The pendulum swung to the use of ice-tong callipers on the theory that if the bone was not transfixed the risk of osteomyelitis was less.

The risk of this method was slipping of the callipers into an adjacent joint with resulting septic joint infection, or dragging of the calliper on the skin and subjacent muscle causing pain, mild infection and scar formation. This was liable to lead to some stiffness of the joint. It was then that transfixion of the bone by a less traumatic method began to come into vogue.

The Kirschner wire is of much smaller diameter than the Steinmann pin and can be gently drilled through the bone. By means of an attached stirrup containing a mechanism to make the wire tense, curving of the wire is prevented and a heavy weight extension can be applied. The risk of osteomyelitis or of superficial sepsis is greatly reduced. Once more the added efficiency of the method of skeletal traction carries with it extra hazards.

The risk of delayed union or true non-union is greatly increased by comparison with the less efficient method of adhesive plaster traction. The fractured ends can readily be pulled apart and a gap formed which cannot be bridged, in spite of Nature's wonderful reparative power.

The surgeon must be very vigilant to avoid this very serious complication, and skeletal traction in any form should not be used unless a portable X-ray service is available and repeated X-ray checks are made.

In the case of a fractured femur, if the Kirschner wire is inserted in the supracondylar region and heavy traction is applied, the wire is liable to "travel", and a condition of a mild sepsis can be set up at its points of entrance and exit, causing scar formation in muscle and subsequent interference with knee joint movement.

If the wire is passed through the head of the tibia, a heavy weight is liable to stretch the main ligaments of the knee joint and to cause symptoms later when the ambulatory stage is reached. As this is the lesser of two evils, it is better, as a rule, to transfix the head of the tibia rather than the supracondylar region of the femur, but the weights used should not be heavier than is necessary just to hold the fracture in position. This lessens the risk of permanent stretching of ligaments.

Open Reduction and Fixation of Fractures.

A considerable proportion of fractures cannot be reduced perfectly by closed methods. The vast majority can be anatomically reduced by open methods. Quite a number need internal fixation to retain the position.

Most metals which are now used for plating or wiring fractures have little irritating effect on the tissues. This is an immense advantage, and, combined with modern chemotherapy, it greatly increases the chances of success in maintaining a perfect reduction until bony union occurs. However, even with these advantages there can be no doubt that open reduction is liable to interfere with and delay bony union. This delay is caused by stripping up blood-supplying tissues from the bone and by cutting actual arteries of supply to the fractured ends. A second feature also comes into play when plates are used. When a bone is fractured, the adjoining ends of the fragments lose their vitality. These necrosed sections are absorbed, and this leaves a small gap between the ends of the fragments. If internal fixation by rigid plates has not been resorted to, it seems likely that the ends will come together and fill the gap. If, however, a metal plate has been rigidly attached to both fragments, this process of sliding together of the fractured ends, after absorption has occurred, is prevented.

The type of plate devised by Eggers, in which the screws enter slots in the plate instead of small screw holes, is at least a partial solution of this problem. To make assurance doubly sure, however, many orthopædic surgeons apply one or more bone grafts as well as the plate in the operation for internal fixation of a recent fracture.

Treatment of Open Fractures.

In the last few years some surgeons have taken advantage of the value of early *débridement* of wounds and of prophylactic chemotherapy to perform the operation of immediate reduction and internal fixation in compound fractures. If complications, particularly sepsis, do not occur, this method saves a great deal of time in hospital and allows comparatively early ambulation.

The matter is still being argued, but in my opinion, owing to the risk and tragedy of bone infection, the weight of evidence is against the method, and the results in the long run are likely to be better when an interval of time is allowed to elapse after *débridement* and skin suture. When the wound is healed, internal fixation is performed. Healing may be facilitated if raw edges are covered, by use of either skin flaps or grafts.

Probably the biggest advance in the treatment of compound fractures since the early part of the 1914-1918 war is this practice of *débridement* of the wound with removal of dead tissue and foreign bodies and thorough washing of the wound within the first few hours after its occurrence. This carries no penalties with it and, unlike a lot of other changes in treatment, is never likely to be abandoned. To expect that this method will produce so sterile a field that an extensive operation can be performed with impunity is, however, asking too much of even a perfect *débridement* and even the latest in antibiotics.

Importance of Careful Examination.

It behoves any medical man who essays to treat a fractured limb to make a careful examination of the whole limb and not to confine his observations to the actual fracture. By doing so he will at times be able to detect complications in the fractured limb which otherwise would be missed.

Failure to notice these complications can readily lay the medical man open to a charge of negligence. He may even be accused of inflicting damage which occurred at the same time as the fracture. It takes only a few minutes to examine the hand or foot of the patient in a search for symptoms of nerve injury.

A common example is radial nerve paralysis in a case of fracture of the humerus. If such conditions are found and recorded before treatment is commenced, the doctor is promptly relieved of any responsibility for the nerve injury.

Another common, though less serious, example of the missed complication occurs in cases of spiral fracture in the lower third of the tibia. This is often associated with a slanting fracture in the region of the neck of the fibula. unless an X-ray picture of the whole length of the leg bones is made, the fibular fracture may be missed and left untreated. A similar safety measure applies to all fractures of long bones.

Conclusion.

If allowance is made for the penalties attaching themselves to modern methods in fracture treatment, advances have been great in this field in the last quarter of a century. Traumatic surgeons have patiently tried out new methods and modifications of old ones in an attempt to sift the grain from the chaff and to arrive at some standardization of treatment. Fracture clinics have been organized and have provided the research laboratories, where painstaking surgeons are trying to assess the value of newer methods. Such activities have been of incalculable value to the victims of trauma.

I am sure that the march of progress in traumatic surgery will not be stemmed because of the occurrence of an occasional inevitable complication.

A. V. MEEHAN,
Brisbane.

Reference.

KINMONTH, J. B. (1952), "The Physiology and Relief of Traumatic Arterial Spasm", *Brit. M. J.*, 1: 59.

British Medical Association News.

SCIENTIFIC.

A MEETING of the South Australian Branch of the British Medical Association was held in the Verco Theatre, Institute of Medical and Veterinary Science, Adelaide, on June 17, 1954, the President, DR. SHOLTO DOUGLAS, in the chair.

Heredity in Disease.

DR. HENRY RISCHBIETH read a paper entitled "Heredity in Disease" (see page 955).

DR. H. R. GILMORE, in opening the discussion, drew attention to the way in which heredity increasingly was forcing its way into the field of general medicine. He cited a recent and important contribution from a team in Professor Pickering's department. There, support was produced for the long-held view that heredity played an important part in determining the occurrence of essential hypertension. Inherited traits which were expressed in the personality of the individual were assuming increasing importance as the part which the psyche played in illness was appreciated. That was underlined in the current interest in psychosomatic illness and research. Dr. Gilmore wondered if in the long run this might not prove to be the bearing of greatest practical importance that heredity had on disease.

DR. F. H. BEARE asked whether it was considered that athletic prowess was an hereditary or an environmental trait; he pointed out that it was not uncommon to find more than one member of some families excelling at a particular sport. He mentioned as an instance the fact that at present three brothers were playing League football in the same team.

Dr. Rischbieth, in reply, said that as in so many other cases there seemed in the case under discussion to be an interplay between heredity and environment. People in such cases were fortunately endowed genetically in relation to the particular attributes required, but in addition training and practice had developed the skills to the maximum. To excel at games a good eye and good coordination of hand and leg movements *et cetera* were required; but those would be insufficient without a favourable environment to allow them to be utilized to the full and the encouragement which some parents might give in greater measure than others.

Dr. Sholto Douglas, from the chair, mentioned the case of two sisters married to two brothers, each of whom produced a hydrocephalic still-born infant, and inquired whether that might be of genetic origin.

Dr. Rischbieth, in reply, said that those might well represent cases of a lethal recessive gene carried by both parents. He cited a somewhat similar case in which a sister and brother had married a brother and his sister respectively; the first couple produced two monsters as the result of four pregnancies and the second one very similar monster. There again a lethal recessive gene in each family was postulated.

Medical Societies.

PÆDIATRIC SOCIETY OF VICTORIA.

A MEETING of the Pædiatric Society of Victoria was held at the Royal Children's Hospital, Carlton, on July 14, 1954. The meeting took the form of a series of clinical presentations.

Coarctation of the Aorta with Other Cardiac Lesions.

Details of two cases of coarctation of the aorta with associated cardiac lesions were presented.

Coarctation of the Aorta and Aortic Regurgitation.

DR. HOWARD WILLIAMS showed a boy, aged twelve years, who had coarctation of the aorta and also aortic regurgitation due to subacute bacterial endocarditis. The boy, who was the first of three children and whose parents were well, had always been active. Early in February, 1954, he had become languid and "off colour" and did not want to play. His appetite failed, and he commenced to lose weight. The symptoms gradually became more severe, and in the middle of April, 1954, small red spots like "little blood blisters" appeared on his legs and finger tips, and he developed pain in his left leg. His medical practitioner made a diagnosis of subacute bacterial endocarditis, as the boy had an enlarged heart, a harsh loud systolic bruit, petechial spots and fever. Two specimens of blood submitted to attempted culture were sterile. Treatment with intramuscular injections of penicillin and oral administration of "Aureomycin" was carried out for six weeks. Some general improvement occurred, but as the boy still looked ill and had a very large heart he was referred to the Royal Children's Hospital at the end of May, 1954.

He was a pale, sick-looking boy with a normal temperature, a pulse rate of 136 per minute and a respiration rate of 20 per minute. His heart was very large, the apex beat being in the fifth left intercostal space, one and a half inches from the nipple line; triple rhythm was audible with a to-and-fro murmur in the aortic area and a blowing systolic bruit over the entire precordial area. The carotid and brachial pulses were forcible, and the blood pressure was 220 millimetres of mercury, systolic, and 110 millimetres, diastolic, in the right arm and 190 millimetres of mercury, systolic, and 95 millimetres, diastolic, in the left arm. The femoral pulses were just palpable. Radiological examination of the chest showed a very enlarged heart, no one chamber being disproportionately enlarged, congested lung fields and a little pleural fluid. The urine was normal. There was no doubt that the child had coarctation of the aorta and aortic regurgitation with cardiac failure, the regurgitation being probably due to subacute bacterial endocarditis affecting the aortic valves. A routine X-ray examination of the chest two years before had not disclosed any abnormality.

Dr. Williams said that treatment with digitalis and "Neptal" had resulted in temporary improvement over a period of three to four weeks, but then the child lost ground and developed further evidence of cardiac failure. He also said that there was no evidence of any residual activity of the endocarditis, as the child was afebrile, the results of four blood cultures were negative, the urine was free of red blood cells and casts, and there were no signs of embolism. The problem was one not of diagnosis but of management. The question was whether resection of the coarcted area in the aorta would relieve the strain on the heart by lowering the blood pressure and diminishing the regurgitation. Theoretically that should happen. If any clinical experience confirmed that, then surgical treatment was desirable even though the operative risk was very great.

It was from that point of view that the patient was being shown at the meeting.

Coarctation of the Aorta with Aortic Stenosis.

DR. MOSTYN POWELL presented the clinical details of a boy, aged ten years, who had first been admitted to the Royal Children's Hospital at the age of four years with left basal pneumonia. He was found to have a congenital heart lesion with a loud systolic bruit audible over the aortic area, and the femoral pulses were noted to be absent. Following this admission to hospital he had repeated attacks of epistaxis, in one of which the hæmoglobin value dropped to 50% and a transfusion was given. At the age of nine years he developed a right basal pneumonia. At present he was well, though the mother reported some recent anorexia. There were no headaches, attacks of epistaxis or limb pains. On examination he was found to be a well-developed boy. The apex beat was in the fifth intercostal space, one inch outside the nipple line. A loud harsh systolic bruit was audible and a thrill was palpable over the aortic area and in the suprasternal notch, where the pulsating vessel was palpable. Femoral pulses were absent, but scapular collaterals were not felt. The blood pressure was 130 millimetres of mercury, systolic, and 80 millimetres diastolic, in the right arm and 125 millimetres of mercury, systolic, and 70 millimetres, diastolic, in the left arm. The condition was regarded as coarctation of the aorta with aortic stenosis. The electrocardiogram showed very slight left axis deviation and marked left ventricular hypertrophy. The angiogram confirmed the presence of coarctation of the localized type and of aortic stenosis.

In presenting the case, Dr. Powell said that no problem of diagnosis was involved as the clinical findings and results of angiocardiography appeared definite. The problem at issue was operation and its type. Was the presence of the coarctation sustaining a high ascending aorta pressure and thus maintaining adequate filling of the coronaries, and would relief of the coarctation significantly diminish the coronary supply? In many parts of the world patients with the two lesions concerned were operated on in routine fashion apparently without harm. However, other people had had unfortunate experiences, such as sudden death at a later date.

Discussion.

DR. R. N. HOWARD opened the discussion and said that 40% of patients with coarctation of the aorta were said to have bicuspid aortic valves. He thought that if one had the combination of two lesions, coarctation and an aortic valve lesion, and one disturbed the coarctation, there might not be enough pressure maintained in the aorta to supply the coronary circulation.

He had had no experience in operating on a patient with the two lesions, but had discussed the question of coarctation and aortic regurgitation with Gross, who had expressed unwillingness to operate because of the bad prognosis. He had since written to Gross about the two patients under discussion and received a reply. Gross stated that in 200 cases he had not had one of coarctation and aortic stenosis. Regarding coarctation and aortic regurgitation he had had three patients with severe regurgitation who died in the early post-operative period. Among 18 patients with minor regurgitation there were no deaths.

Dr. Howard thought that Dr. Williams's patient might be benefited considerably by operation on the coarctation; the aortic ring might contract and the regurgitation then improve. However, the patient's condition had deteriorated considerably in the last few days, and he thought the operation should wait until the patient improved again. If he did not improve, and the parents were aware of the great risk, he felt that the patient should be operated upon.

DR. C. J. O. BROWN in discussing the condition of coarctation and severe aortic regurgitation said that he had operated on one boy of sixteen years with those lesions. The boy had a blood pressure in the arm of 200 millimetres of mercury, systolic, and 70 millimetres, diastolic. His convalescence was untroubled, and two and a half years later he was alive and vastly improved. One year after operation the blood pressure had been 160 millimetres of mercury, systolic, and 50 millimetres, diastolic.

Dr. Brown said that he had operated on five patients suffering from coarctation with mild aortic regurgitation, and all had made an uncomplicated recovery. With regard

to the particular case under discussion he agreed that the boy's only chance was to be operated on.

Dr. Brown had operated on two subjects of coarctation with aortic stenosis. One girl in her early twenties with a systolic blood pressure of 190 millimetres of mercury had survived operation on the coarctation and was well for eight months, her systolic blood pressure falling to 110 millimetres of mercury. However, she had then developed anginal pains, and four months later died of coronary thrombosis. Dr. Brown showed a lantern slide picture of the aortic valves, which were solidly calcified with a quarter of an inch of calcium. The valve was not bicuspid. The other patient, a girl, was six and a half years old at the time of operation on the coarctation, and her systolic blood pressure was 180 millimetres of mercury. She did well, and the blood pressure fell to 120 millimetres of mercury, systolic, and 80 millimetres, diastolic. However, eighteen months after operation she dropped dead. Dr. Brown showed the specimen of the aortic valve, which consisted of a tiny orifice surrounded by dense fibrous scar tissue. It would, in his opinion, have been possible to divide that with a knife, and the valve might have stayed open, but he thought that dilatation would not have done any good. He was not satisfied that aortic valvulotomy was going to be a successful operation for congenital aortic stenosis or for the calcified rheumatic valve either.

At the present time he felt that he did not know what to do about the combination of the two lesions. He had three patients not yet operated on, but would have to make a decision in the near future. The two patients cited might have died without operation, as it was well known that patients with aortic stenosis did that.

He thought that if the heart had not been able to adapt itself to the altered coronary circulation, the patients would have died more quickly. Dr. Brown concluded by saying that with regard to Dr. Powell's case of aortic stenosis and coarctation there would be no harm in delaying the decision until more was known of the surgery of aortic stenosis.

DR. I. MCCONCHIE said that he thought that patients with coarctation and regurgitation should undergo operation. In the present case there was severe regurgitation, but it had probably not been in existence for long, and the left ventricle probably was not irrevocably harmed. Relief of the coarctation by reduction of pressure and diminution in the size of the aortic ring might tend to bring about diminution in regurgitation.

With regard to the second case, he thought that an angiogram might show up the degree of stenosis. Both lesions should be dealt with by operation. He had seen Brock operate on six such patients. The aortic stenosis was relieved by valvulotomy through the left ventricle. When the coarctation operation was being performed, pressures should be taken across the aortic valve. If the pressure gradient was significant, valvulotomy should be carried out later.

DR. K. MORRIS thought that both these cases presented difficult problems and both patients had a limited expectation of life whatever was done. However, death could be delayed by removing the coarctation. He did not think that operation on the coarctation would hasten death in stenosis.

Dr. Williams, in reply, thanked the speakers, and said that his patient would be operated upon if and when his condition could be improved.

Dr. Powell said that with regard to his case he thought that it would be advisable to operate on the coarctation, take pressure gradients, and then wait and operate on the stenosis later under hypothermia and direct vision.

Caffey's Infantile Cortical Hyperostosis.

DR. FRIEDA PLARRE, on behalf of DR. MURRAY CLARKE and herself, presented the clinical details of a case of Caffey's infantile cortical hyperostosis (see page 967).

Dr. Clarke said that the case was one in which the diagnosis had been made by the radiologist, but he would like to comment on one or two points in the history. The mass was the shape and size of the scapula but had a soft surface, and the patient's temperature was 99·6° F. The baby had had chemotherapy in the country, and the differential diagnosis lay between osteomyelitis, trauma and neoplasm. There was no history of trauma, and the mass was never painful or tender. Osteomyelitis was favoured. At biopsy the muscle and bone appeared macroscopically normal. If the condition had been known, biopsy would not have been performed. In future the condition would be looked for.

DR. J. COLEBATCH said that one of the writers on the condition stressed the argument in favour of an inflammatory ætiology. He would like to know whether the case which Dr. Plarre had mentioned as being diagnosed at the thirty-first week *in utero* was associated with any symptoms in the mother.

Dr. Plarre replied that there was no ætiology suggested for the case, which was diagnosed *in utero*. The pathology and ætiology of the condition were as yet completely unknown.

Cretinism Diagnosed at an Early Age.

DR. GWEN HEWITT presented the clinical details of a male child, three and a half months of age, who was very slow with his feeds. This was attributed by the mother to a blocked nose. Feeding would take an hour, and then the baby was exhausted. Breast feeding was continued for the first six weeks of life, but only three to four ounces were gained each week. "Nestlé's" condensed milk mixture was then substituted; but as only half his calculated requirement was taken, the baby did not gain weight. He had always been constipated, the mouth was always open, the tongue large and the skin dry. Milestones were retarded. He smiled at the age of three months and became vocal at three and a half months; head control was poor at three and a half months. His birth had been normal, the birth weight being seven pounds 14 ounces, and the mother was well during the pregnancy. There was one sister, aged four and a half years, who was healthy apart from asthma. The father also suffered from asthma, but there was no thyroid disorder in the family or relatives.

Examination revealed a pale wasted baby with a dry yellowish wrinkled skin and some puffiness round the eyes. There were no supraclavicular pads of fat, nor was there any increase in subcutaneous fat, although the skin was dry, thick and inelastic. A large broad tongue was visible through the open mouth, and there were wrinkles round the mouth suggesting healed fissures. A large umbilical hernia was present, and around the anus was excoriation of the anal skin with fissuring. The rectal temperature was 97° F., and the weight was 11 pounds six ounces.

The blood cholesterol content was 183 milligrammes per 100 millilitres and the alkaline phosphatase content seven units. The results of blood Wassermann and Kahn tests were negative. X-ray examination of long bones showed gross epiphyseal retardation at all areas with some increased flaring of the metaphyses of the long bones.

As the patient lived in the country, five weeks elapsed before treatment was instituted. In that time neither sucking nor weight had improved despite the introduction of a stronger feeding. An eczematous rash had spread over the face. The bowels opened only every third day, and the rectal temperature was still subnormal. At that stage administration of thyroid, a quarter of a grain three times a day, was instituted. In three weeks improvement was already obvious. He was livelier, happier, and eating and drinking better. The weight had increased by 27 ounces, and the bowels opened five times a day. The rectal temperature was 97·8° F. and the pulse rate 120 per minute. The skin had not improved greatly. The dose of thyroid was not altered.

By the age of six and a half months there was further definite improvement. The child laughed and babbled and could recognize his parents. Head control was better, the skin was less dry and the tongue was smaller. The rash, however, remained. The umbilical hernia had practically disappeared. The pulse rate was 130 per minute and the rectal temperature 98·4° F. Weight had increased by a further 17 ounces in three weeks. An X-ray examination showed epiphyseal growth to be still grossly retarded. The alkaline phosphatase level had risen to ten units, and the blood cholesterol level had fallen to 130 milligrammes per 100 millilitres.

At the age of seven and a half months the baby could lift his head from the couch in the prone position but not in the supine. The voice was still rather hoarse, but the umbilicus no longer protruded. There were two formed motions each day. Weight gain was proceeding satisfactorily, his weight being 15 pounds and 13 ounces, and his length was twenty-five and seven-eights inches.

DR. H. N. B. WETTENHALL presented the clinical details of a female child who had been first examined at the age of nine weeks with the symptoms of diarrhœa for forty-eight hours and vomiting for twenty-four hours. The bowels had been constipated prior to that episode, but for two days they had opened frequently, the motions containing slime but no blood. Prior to the illness the baby had been pale and thin, slept a lot and cried rarely. Examination revealed the typical appearance of a cretin with a dry skin, slightly protruding tongue, supraclavicular pads of fat and umbilical

hernia. The baby showed a moderate degree of dehydration, and the temperature would not rise above 95° F. The pulse rate was 84 per minute and the respiration rate 18 per minute.

The baby was treated in the routine manner for gastro-enteritis, and that subsided. The cretinism was treated at first with thyroid, one-eighth of a grain twice a day, but after forty-eight hours that was changed to one-quarter of a grain daily.

There were no pathogenic organisms in the stool. X-ray examination of the bones showed no epiphyses of the upper part of the tibia, lower part of the femur or cuboid bones.

The blood cholesterol level three weeks after admission to hospital was 236 milligrammes per 100 millilitres.

The baby's temperature did not rise to a normal level until four days after admission to hospital. The pulse rate rose to 100 per minute after five days and to 120 per minute after twelve days. The dose of thyroid had been steadily increased, and the baby was now having three-quarters of a grain daily. Her appearance had greatly improved, she took her feedings well, and she was beginning to show an interest in her surroundings. It was proposed to increase the dosage of thyroid by a quarter of a grain every three weeks until toxic signs developed.

Dr. Wettenhall went on to say that the diagnosis of cretinism presented two main problems. Firstly, there were those patients who were wrongly called cretins, such as the backward child, the fat child, and the baby with the ugly face, whether it was due to gargoylism, mongolism or purely familial characteristics. Secondly, there were those cretins who were not recognized as such, being diagnosed as suffering from infantilism, failure to thrive or anæmia. Diagnosis rested, firstly, on functional changes, which included the slow pulse, depressed body temperature, poor muscle tone and obstinate constipation, secondly, on failure of normal growth, which was shown by the small size of the child and the delayed appearance of epiphyses, and, finally, on the facial appearance of the child, whose puffy coarse features and large protruding tongue helped to point to the diagnosis.

Investigations other than X-ray examination of epiphyseal regions were of little value in diagnosis. The serum cholesterol level normally presented a very wide variation, and estimation of the basal metabolic rate was obviously not possible in the small child.

Treatment depended on giving sufficient thyroid. This should be increased until toxic symptoms such as diarrhœa and loss of weight were present. It was usually possible to obtain normal physical development in the children, but it was generally agreed that progress in mental development was not so uniformly obtained. Almost all the authorities agreed that a significant proportion of cretins remained mentally backward.

DR. R. SOUTHBY, opening the discussion, said that with regard to mental development in cretins he thought that the ultimate result of treatment was unpredictable. His usual practice was to push treatment to the limit of tolerance and then to work back. However, even then one could not tell which patient would do well as far as mental development was concerned. One of his most severely affected patients, who had started treatment at nineteen months of age, was now twenty-two years old and an engineer. Another, whose condition was not so severe in babyhood, was now an imbecile.

DR. L. P. WAIT said that mental development depended to a certain extent on the family stock. He had treated one child for sixteen years, and the child was now normal mentally and physically.

DR. J. COLEBATCH said that it was important to diagnose and treat early. They all knew that it was easy to miss the diagnosis. Cases easily missed were those in which the patient presented with other things such as eczema or constipation. In babies who were mentally deficient the possibility of hypothyroidism needed to be excluded. With regard to special diagnostic tests he thought that the serum alkaline phosphatase estimation was more useful than the cholesterol estimation, and as useful as X-ray examination of the long bones. In treatment one should aim at adequate dosage early. The slowly increasing dose over three months was not good, and the dangers of overdosage were slight.

DR. A. P. DERHAM commented on two points. He described the signs of overdosage as loss of weight, diarrhœa and excitability. He thought that there was no need to give the thyroid preparation in three doses daily; it could all be given in the morning, that being a helpful point to the patient.

DR. K. CAMPBELL also thought that the end results were not entirely satisfactory. In none of her cases were the patients entirely normal, even when treatment was started very early.

Dr. Wettenhall, in reply, said that there did seem to be a doubt about the question of mental development. He thought that a lot depended on the genetic background. He considered that partial thyroid deficiency was a definite clinical entity.

A Rare Triad of Congenital Anomalies.

DR. F. D. STEPHENS presented details of a patient showing a rare triad of congenital anomalies—megaureters, absence of abdominal musculature and undescended testes. He said that the association of megaureters with absence of or grossly thinned-out abdominal musculature and undescended testes was a regularly occurring though rare triad of congenital abnormalities. Those anomalies had been reported in over sixty cases.

He had seen and studied, in various ways, three patients with such a condition. One of them was a boy, aged six months. He was a healthy, lively, first-born baby, seven and a half pounds in weight, and the result of a normal pregnancy and labour. There were no known abnormalities in the family. The presenting and striking feature was the appearance of the abdominal skin, which was loose, crinkled and pendulous, permitting the abdominal viscera to bulge and sag with the changing posture of the child. The musculature appeared to be absent or very much weakened all over the abdomen, but more particularly in the right flank. Since he had been first examined, the skin had become more puckered and thickened by the invasion of the subcutaneous layer with fat. The left side of the abdominal wall appeared to have become a little stronger. The testes were impalpable, but the genitalia were otherwise normal in appearance. The bladder was readily palpable, extending in conical shape to the umbilicus, and the ureters were vaguely palpable.

The urinary tract had been investigated further, and the blood urea content was normal. Micturition was performed intermittently without straining or discomfort and with a stream of good normal force and calibre. Micturition cystourethrography disclosed that the bladder emptied completely. It also showed a widely dilated prostatic urethra, a larger than normal bladder with a blind urachal extension to the umbilicus, and reflux into the utriculus or ejaculatory duct and into both ureters. The ureters were very large in calibre and grossly convoluted. The pelvis of the left kidney was considerably dilated above normal size, but the calyces were not clubbed. The urethra distal to the prostatic urethra was of normal calibre. A slide demonstrating the micturition cystourethrogram in lateral view was shown to demonstrate these features.

Excretion pyelography showed that the excretion of iodide occurred in good concentration in ten minutes into both kidney pelves. The calyces were normal in number and were not clubbed. The iodide was diluted too much by the urine to be recognizable below the middle of the enlarged ureters.

Cystoscopy showed gross dilatation of the prostatic part of the urethra; the verumontanum, if present, was tucked so deeply in the posterior pocket that it could not be identified. The bladder neck was widely open, and the trigone was very large, the ureteric orifices being situated so far from the bladder outlet that they appeared to be almost on the dome. The orifices were widely open and patulous, and the bladder mucosa was pale, smooth and not trabeculated.

The calibre of the penile urethra was insufficiently large to permit the introduction of the smallest catheterizing cystoscope, so the retrograde pyelograms and ureteral emptying times were not as yet available.

From information derived from this child's case and from two others which he had investigated, one that of a happy, strong child of eighteen months under the care of Mr. T. T. Higgins at the Hospital for Sick Children, London (described in "The Urology of Childhood", by Higgins *et alii*), and one that of a baby who had died at birth and from whom post-mortem specimens were shown to him by Dr. Abrahams, of the Queen Victoria Hospital, to whom he was grateful, Dr. Stephens made the following remarks. The urethra in all three cases was grossly enlarged in its prostatic portion; the specimen showed a very small verumontanum, prostatic tissue and two *vasa deferentia* without any evidence of vesicles. The membranous part of the urethra was of normal calibre. The bladder was enlarged with a blind urachal extension, and the ureteric orifices were wide in calibre and situated at the extremes of two long attenuated cornua of the very large trigone. The ureters were very tortuous, thin-walled and large in calibre, tapering to the pelves of the kidneys.

The kidneys in the specimen examined had the following features. On the right was a blind hydronephrotic sac as large as the bladder with a small rim of kidney tissue at either pole; on the left the kidney was very small, the upper half being solid kidney tissue and the lower half a thin sac in communication with the ureter.

Dr. Stephens said that the explanations of the triad were varied. It was still not known whether the urinary abnormalities occurred as a result of the absence of the abdominal musculature or vice versa. Bladder-neck obstruction accounting for the dilatation of the urinary tract had been described in some cases.

In many of the children the large ureters permitted free reflux, and that meant that there was constantly considerable residual urine in the urinary tract. That led to infection. Infection in the first two to three years must be combated by chemotherapy, but after that age regular triple micturition should be started with a view to eliminating the residual urine.

Renal hypoplasia and pyelonephritis were probably the most important causes of death in the children affected. Dr. Stephens was hopeful that the triple micturition régime would help to stave off the infections.

Dr. J. McCoy asked whether the pathological lesions in such a case might not be due to a urethral valve. All the findings could possibly be explained by the effect of obstruction, such as large bladder and ureters produced by distension, poor abdominal muscle development and delay in the descent of the testes. During labour perhaps the urethral valve was broken down. He said that he had met with one similar case at post-mortem examination in which the remnants of a urethral valve were seen.

Dr. Stephens replied that there were many theories regarding the ætiology of the condition. He could imagine obstruction at some stage, which might have been broken down, but it was the rule rather than the exception to get obstruction with normal abdominal musculature. He thought, however, that a delicate membrane rather than a valve might be the cause of such an obstruction.

Dr. P. Jones said that he had encountered three such cases. Two of the patients had been uræmic at birth, and both had died during the first week of life. They had some obstruction, but it was not valvular. The third patient had no obstruction. Dr. Jones asked Dr. Stephens what he thought was the prognosis in these cases.

Dr. Stephens, in reply, thought that there was probably obstruction present in some cases, but he had not seen it himself. He did not think that there was obstruction in the case under discussion. He said that he was not sure of the mortality of the condition. Some subjects lived up to the age of twenty years, but not beyond. They might die early of hypoplasia of the kidneys. He thought that the prognosis in the present case might be quite good if infection could be controlled.

Out of the Past.

In this column will be published from time to time extracts, taken from medical journals, newspapers, official and historical records, diaries and so on, dealing with events connected with the early medical history of Australia.

MR. DENIS CONSIDEN TO SIR JOSEPH BANKS (BANKS PAPERS).[1]

[From "The Historical Records of New South Wales", Volume I.]

Port Jackson,
November 18, 1788.

SIR: From the intimacy which subsisted between you and my friend Capt. Chas. Hamilton, I have taken the liberty of sending home some birds and a Kangaroo skin, properly stuffed, to your care to be forwarded to him as soon as possible. At the same time I beg your acceptance of five birds and a Kangaroo skin—all properly prepared and stuffed. I have likewise sent you two living opossums (one for you and the other for Captain Hamilton) and two beautiful paroquets alive (one for Mrs. Charles Hamilton and the other for your daughter). I sincerely wish they may reach you safe. Understanding you were a naturalist as well as a botanist, I have sent you some bulbs viz. two species from S. America, and some flower seeds (such as I could at present collect in this country) and specimens of two sorts of gum, the production of this country, the one red and the other yellow. The first is the red astringent gum well known in England: the other I have taken the liberty of naming the balsam to be of New South Wales. These I have used medicinally, and found them to answer my most sanguine expectations. I have sent you some of the sweet tea[1] of this country which I recommend, and is generally used by the marines and convicts. As such it is a good antiscorbutic as well as a substitute for that which is more costly. This country produces a variety of flowers and shrubs totally unknown in Europe and five or six varieties of wild myrtle, some of which I have sent to you dried. An infusion of the leaves of one sort is a mild and safe astringent in the dysentery. We have a large peppermint-tree which is equal if not superior to our English peppermint. I have sent you a specimen of it. If there is any merit in applying these and many other simples to the benefit of the poor wretches here, I certainly claim it, being the first who discovered and recommended them.

Many of the shrubs are now in bloom and many more have not yet ripened their seed. Therefore, I cannot send you that variety I could wish, but I will make it my business during my residence here to send you some by every opportunity should it be pleasing to you.

You are probably surprised I have not given you some account of the country &c. when I have taken the liberty of addressing you at all. For this I beg leave to refer you to Capt. Hamilton, to whom I have given a short sketch of it together with my opinion. I had forgot to say that the red gum is produced by two very different sorts of trees, and that the yellow gum is the production of a small tree of the palmette kind, the seed of which I have sent to you. It grows on a stalk from 6 to 10 feet long, and very much resembles a cone, out of the centre of the top of the tree, which is from 3 to 7 feet high, and the circumference from 18 to 24 inches: the external surface appears as if burned, but upon examination, it is only a black vein, which, if powdered, becomes of a red colour.

I am, &c.,
D. CONSIDEN.[2]

[1] From the original in the Mitchell Library, Sydney.

[1] The native sarsaparilla.

[2] Denis Considen arrived in the first fleet as surgeon on *Scarborough*; he returned to England in 1793.

Correspondence.

THE COLLEGE OF GENERAL PRACTITIONERS: NEW SOUTH WALES FACULTY.

SIR: The College of General Practitioners held a post-graduate week-end at Dormie House, Moss Vale, on November 5, 6 and 7. I attended from Victoria, and found the lectures most instructive. Lectures were given: "Thrombo-Embolic Disease", Dr. A. W. Morrow; "Symptoms After Cholecystectomy", Dr. Norman Wyndham; "Induction of Labour: Its Indications and Methods", Dr. Robert Gill. On November 7 there was question session, which was followed by a meeting of the College. This meeting gave me an opportunity to meet colleagues from another State, and I appreciated their cordial welcome. The College intends to hold further post-graduate meetings next year.

Yours, etc.,

Dawney Street,
Alexandra,
Victoria.
November 19, 1954.

T. M. HENDRY.

YOUNG DOCTORS AND SPECIALIZATION.

SIR: Dr. O. H. Green states (M. J. AUSTRALIA, October 30, 1954): "It appears that, after two years in a teaching hospital and the acquisition of a diploma by examination, a young graduate may register as a specialist in surgery and take the responsibility for major procedures without more ado."

Dr. Ewen Sussman says (M. J. AUSTRALIA, November 20, 1954): "In recent years good hospital posts have become impossible to achieve without a post-graduate degree. Even with this degree such appointments are by no means certain, as many young Fellows of the Royal College of Surgeons in this city can confirm. . . . In Britain most specialists commence their training at graduation."

In Queensland the law places no restriction on the practice of surgery by general practitioners. Some little time ago an old and respected practitioner said to me that "Ned Kelly had nothing on some young graduates". He was referring to the practice of surgery by recently qualified practitioners.

These various quotations raise important problems on the practice of surgery and one that our legislators have too long delayed in providing that the practice of surgery should be carried out under conditions that are as safe as possible for the general public. At the same time they should give attention to the importance of individuals who aspire to be specialists and lay down conditions under which surgery may be practised as a specialty. In a State like Queensland where distances are very great the problem is not easy of solution, but until it is tackled much harm can be done to the individuals that make up the community. Is it not time that the representatives of the profession in Australia gave the matter some attention?

Yours, etc.,

E. S. MEYERS.

The University of Queensland Medical School,
Brisbane,
November 22, 1954.

SIR: Please allow me to support the remarks of Dr. Owen H. Green (M. J. AUSTRALIA, October 30). However, the position is a difficult one. If the young graduate does not get his higher qualification and training soon after graduation, it becomes harder and harder to do and get. If he does not grab a hospital appointment whilst he is still seen, he may be forgotten and miss altogether. He is wrongly taught or encouraged to believe that specializing is the top of the profession—all branches equal.

To me it is a tragedy, for students, doctors and patients, the full effect of which will not be felt for years, that many of our young men are being appointed specialists to teaching hospitals upon the acquisition of a higher degree and some service to a hospital and in many cases a narrow-eyed service to one hospital only.

The remedy lies with the teaching hospitals and the University. As Dr. Green says, all would-be specialists should have to serve an obligatory period in the outside cold hard world before their appointment is made or confirmed.

This problem is mixed up with Sir Herbert Schlink's recent statement in *The Sydney Morning Herald* that no more hospitals should be built until the teaching hospitals are 100%. All will agree they should be 100%, but could not the specialist, general practitioner and student learn more and the patient in many cases benefit more from being treated near her own home by her own doctor guided by the specialist accompanied by some students?

At present, I think to the loss of all concerned, the patient loses the personal touch and becomes a disease and not a human being all too soon.

Yours, etc.,

A. M. MACINTOSH.

Cronulla,
New South Wales,
November 18, 1954.

REGISTRATION OF MEDICAL PRACTITIONERS.

SIR: I have always held that the Medical Acts of each State of Australia, in so far as medical practice and the registration and licensing of medical practitioners are concerned, are invalid, according to Section 92 of the Australian Constitution. The New South Wales Government has recently created what amounts to a licensing fee of £1 1s. per year for each doctor to have his name placed on the New South Wales medical register. This would appear to be also invalid. Most doctors in capital cities of each State have patients undertaking special interstate journeys for consultation purposes, in other words, medical practice is an interstate business, and therefore beyond the powers of State Governments. It is interesting to note that on Wednesday last, the Privy Council in England ruled that the New South Wales Government (or any other State Government) had no power to license interstate transport. I believe it is important to keep these points in mind, as in a few years State Governments may be demanding £10 or £20 for a doctor to be licensed and have his name placed on the medical register.

Yours, etc.,

A. LESLIE WATSON.

Sydney,
November 19, 1954.

ATOMIC WARFARE.

SIR: A leading Australian medical man has been quoted in the Press as saying that protective measures could be adopted against atomic attack and that the long-range effects of radiation were not as serious as at first thought. However, it is obvious that for the great majority there could be no safety from atomic attack, and leading British and American scientists believe there may already be serious genetic changes as a result of the test explosions.

The facts show that if a single hydrogen bomb from plane or rocket landed on Melbourne it would in a flash utterly destroy all buildings and life in the inner and middle suburbs. This would include all the major hospitals, ambulance stations and the majority of the doctors, nurses and other medical staff. For several days afterwards an area of a hundred miles diameter around the city would be lethal to anyone not under cover. After this period what could a few country medical services do for the hundreds of thousands of injured in the city area, with no shelter, water or communications?

Obviously there is only one protection against atomic warfare, and that is to ban it. The medical profession with its mission to save life should be in the lead of the movement to abolish modern mass murder weapons and to bring pressure on our governments to divert their energies and resources instead to the still vast problems of disease and undernourishment.

Yours, etc.,

ROLAND GOOD.

238 View Street,
Bendigo,
Victoria.
October 19, 1954.

PHÆOCHROMOCYTOMA OF THE SUPRARENAL GLAND.

SIR: We have read with interest the article by Dr. M. G. Whitehead on phæochromocytoma of the suprarenal gland in your issue of November 6 and consider that he has done a great service in showing that these tumours have often escaped detection during life. Since phæochromocytoma causes one of the few types of hypertension which can be cured, it is important that the diagnosis should not be missed. However, we take issue with Dr. Whitehead on his statement: "At present, if such a condition is suspected, the patient is subjected to a large number of uncomfortable, expensive and even dangerous investigations. . . . Lack of a simple and reliable confirmatory test is thus one reason for failure of diagnosis." This may have been so in the past, but at present the position is far different.

There are two valuable screening tests which cause no discomfort or danger to the patient. The first is the hypotensive action of intravenously injected "Regitine" (see Barnett and Fowler, 1952). The second is the assay of noradrenaline in the urine. This procedure is being used at the Baker Medical Research Institute and has enabled us to confirm the presence of phæochromocytoma in two patients in Tasmania, one in New South Wales and two in Victoria. In three of these four cases, the tumours have been successfully removed at operation.

Since hypertension is a common disease and phæochromocytoma a rare one, it is a matter of practical importance to decide which patients should be investigated for the latter condition. We suggest that a "Regitine" test should be done (*a*) in all patients with clinical features (such as paroxysms of hypertension, hypertension associated with sweating or vasomotor disturbances) suggesting a phæochromocytoma, (*b*) young persons with severe hypertension, especially if in the "malignant phase", and with no established cause, and

(c) severe hypertension of recent onset. If the "Regitine" test is "positive" (that is, if the diastolic blood pressure falls by 30 millimetres of mercury or more), the urine should be assayed for nor-adrenaline. It is only when the presence of a tumour has been demonstrated or strongly indicated by these tests that one is obliged to perform the more "uncomfortable" procedures of perirenal air insufflation or aortography to localize the tumour.

We shall be very pleased to cooperate with any practitioner who has a suspected cases of phæochromocytoma.

Yours, etc.,

A. J. BARNETT, M.D.
G. A. BENTLEY, Ph.D.

Baker Medical Research Institute and Alfred Hospital Clinical Research Unit, Melbourne.
Undated.

Reference.

BARNETT, A. J., and FOWLER, R. (1952), "The Action of 'Regitine' in Man with Special Reference to its Adrenergic Blocking Action", *Australasian Ann. Med.*, 1: 109.

Naval, Military and Air Force.

APPOINTMENTS.

THE undermentioned appointments, changes *et cetera* have been promulgated in the *Commonwealth of Australia Gazette*, Number 74, of December 2, 1954.

AUSTRALIAN MILITARY FORCES.

Citizen Military Forces.

Northern Command: First Military District.

Royal Australian Army Medical Corps (Medical).—To be Temporary Major, 15th October, 1954: 1/10316 Captain H. W. A. Forbes.

Eastern Command: Second Military District.

Royal Australian Army Medical Corps (Medical).—2/183732 Captain (provisionally) G. W. de Meyrick relinquishes the provisional rank of Captain and is transferred to the Reserve of Officers (Royal Australian Army Medical Corps (Medical)) (2nd Military District) in the honorary rank of Captain, 28th February, 1954. To be Captain (provisionally), 14th October, 1954: 2/116143 Ian Roger Vanderfield.

Southern Command: Third Military District.

Royal Australian Army Medical Corps (Medical).—3/114023 Major (provisionally) C. A. Jones ceases to be seconded whilst in the United Kingdom, 1st July, 1954. 3/50211 Captain (Honorary Major) P. Kaye is appointed from the Reserve of Officers, and to be temporary Major, 1st September, 1954. To be Captain (provisionally), 7th October, 1954: 3/101027 Donald Gordon Macleish.

Western Command: Fifth Military District.

Royal Australian Army Medical Corps (Medical).—3/101022 Captain (provisionally) A. G. Mathew relinquishes the provisional rank of Captain and is transferred to the Reserve of Officers (Royal Australian Army Medical Corps (Medical)) (5th Military District) in the honorary rank of Captain, 4th October, 1954.

Reserve Citizen Military Forces.

Royal Australian Army Medical Corps.

1st Military District.—To be Honorary Captains, 11th October, 1954: Brian Frederick Charles Smith and William Ernest Orford.

2nd Military District.—To be Honorary Captains: Ronald McKay Gray, 23rd August, 1954, Don John Deller, 20th September, 1954, and William Mortimer Kelly, 4th October, 1954.

3rd Military District.—To be Honorary Captain, 13th September, 1954: Robin Charles Winfield Williams.

ROYAL AUSTRALIAN AIR FORCE.

Permanent Air Force: Medical Branch.

Flight Lieutenant (Temporary Squadron Leader) (Acting Wing Commander) D. A. S. Morgan, O.B.E. (04398), is transferred from the Active Citizen Air Force and appointed to a permanent commission, 24th September, 1954, with the rank of Squadron Leader and seniority in that rank as from

DISEASES NOTIFIED IN EACH STATE AND TERRITORY OF AUSTRALIA FOR THE WEEK ENDED NOVEMBER 20, 1954.[1]

Disease.	New South Wales.	Victoria.	Queensland.	South Australia.	Western Australia.	Tasmania.	Northern Territory.	Australian Capital Territory.	Australia.
Acute Rheumatism	5(2)	6(3)	5(5)	..	..	..	..	..	16
Amœbiasis	..	..	..	..	..	..	..	..	..
Ancylostomiasis	..	..	..	..	..	..	..	..	..
Anthrax	..	..	..	..	..	..	..	..	..
Bilharziasis	..	..	..	..	..	..	..	..	..
Brucellosis	..	1	..	..	..	1	..	..	2
Cholera	..	..	..	..	..	..	..	..	..
Chorea (St. Vitus)	..	2(1)	..	..	..	..	..	..	2
Dengue	..	..	..	..	..	..	..	..	..
Diarrhœa (Infantile)	6(3)	12(12)	16(9)	..	..	..	..	..	34
Diphtheria	1(1)	2(1)	3(2)	..	3(3)	..	..	..	9
Dysentery (Bacillary)	..	2(1)	4(2)	..	..	..	1	..	7
Encephalitis	1	1(1)	..	..	..	..	..	..	2
Filariasis	..	..	..	..	..	..	..	..	..
Homologous Serum Jaundice	..	..	..	..	..	..	..	..	..
Hydatid	..	..	..	..	..	..	..	..	..
Infective Hepatitis	80(33)	46(28)	..	..	2(1)	..	3	1	132
Lead Poisoning	..	..	..	..	..	..	..	..	..
Leprosy	..	..	..	..	..	..	1	..	1
Leptospirosis	..	..	1(1)	..	..	..	..	..	1
Malaria	..	..	2(2)	..	..	..	..	..	2
Meningococcal Infection	3(1)	1	1(1)	..	1	..	..	..	6
Ophthalmia	..	..	..	..	2	..	..	..	2
Ornithosis	..	..	..	..	..	..	..	..	..
Paratyphoid	..	..	..	..	..	..	..	..	..
Plague	..	..	..	..	..	..	..	..	..
Poliomyelitis	5(2)	12(8)	10(3)	8(2)	..	..	..	..	35
Puerperal Fever	..	..	1	..	..	..	..	..	1
Rubella	..	31(24)	..	..	27(18)	..	..	..	58
Salmonella Infection	..	..	..	..	1(1)	..	..	..	1
Scarlet Fever	26(14)	32(20)	3(1)	10(8)	3(1)	..	..	..	74
Smallpox	..	..	..	..	..	..	..	..	..
Tetanus	..	..	1(1)	..	..	..	..	..	1
Trachoma	..	..	..	..	2	..	..	..	2
Trichinosis	..	..	..	..	..	..	..	..	..
Tuberculosis	40(25)	19(13)	29(15)	11(8)	7(5)	4(1)	4	..	114
Typhoid Fever	2(2)	..	..	..	..	..	..	..	2
Typhus (Flea-, Mite- and Tick-borne)	..	..	3	..	..	..	..	..	3
Typhus (Louse-borne)	..	..	..	..	..	..	..	..	..
Yellow Fever	..	..	..	..	..	..	..	..	..

[1] Figures in parentheses are those for the metropolitan area.

6th June, 1951, retaining the acting rank of Wing Commander.

The following Flight Lieutenants are granted the acting rank of Squadron Leader, 1st June, 1954: G. S. Radford (025626), A. I. Lane (0210562).

Post-Graduate Work.

NAPT COMMONWEALTH FELLOWSHIP.

THE National Association for the Prevention of Tuberculosis is offering for 1955-1956 a new Commonwealth Fellowship of the value of £350 to enable a medical graduate to do post-graduate study in tuberculosis in the United Kingdom. The intention of the award is to provide training and experience for a doctor who will subsequently play his part in the control of tuberculosis in his own country, and the course of study in Great Britain should last at least three months. Full particulars can be obtained from The National Association for the Prevention of Tuberculosis, Tavistock House North, Tavistock Square, London, W.C.1, and applications should be received not later than March 31, 1955. The successful candidate will be required to arrive in the United Kingdom prior to June 20 of that year if possible. This Fellowship is in addition to the Hunter Commonwealth Scholarship (value £350) already announced.

Notice.

THE COLLEGE OF RADIOLOGISTS OF AUSTRALASIA.

THE following candidates were successful in passing the August examination of The College of Radiologists of Australasia, Part II: Dr. Shirley Roberts (Victoria), Dr. J. J. Power (Queensland), Dr. E. A. Lennon (New South Wales), Dr. N. D. Johnston (South Australia), Dr. J. Bell (New South Wales).

Medical Prizes.

PRIZE FOR MEDICO-SURGICAL FILM.

THE annual prize offered by *La presse médicale* for a medico-surgical film, amounting to 100,000 francs (with the possibility that it may be divided) and various other awards, will be presented as usual during the last session of the course in "*Actualités médico-chirurgicales*" at the Faculty of Medicine of Paris in March, 1955. The prize is awarded only to amateurs for films not previously published, not subsidized and not produced by any laboratory or firm. The films will be judged on their instructional as well as on their cinematographic qualities. Silent or sound films, and films in colour or in black and white, may be entered; but all films must be of 16 millimetre size.

Applications should be forwarded as soon as possible, addressed to *La presse médicale*, 120 Boulevard Saint-Germain, Paris, VI°. Special instructions will be given about the dispatch of films, which must reach Paris by February 28, 1955, the closing date.

Nominations and Elections.

THE undermentioned have applied for election as members of the South Australian Branch of the British Medical Association:

Scholz, William Herbert, M.B., B.S., 1954 (Univ. Adelaide) (qualified 1953), 13 Malcolm Street, Dunleath, South Australia.

Lister, James Dick, M.B., B.S., 1954 (Univ. Adelaide) (qualified 1953), 14 Pembroke Place, Colonel Light Gardens, South Australia.

The undermentioned has been elected as a member of the South Australian Branch of the British Medical Association: Stanbury, Dennis George, M.B., B.S., 1954 (Univ. Adelaide) (qualified 1953).

Medical Appointments.

Dr. Annie Winifred Wall has been appointed honorary anæsthetist, with the status of honorary physician, to the Royal Adelaide Hospital.

Dr. J. A. Ferris has been appointed honorary anæsthetist, with the status of honorary assistant physician, to the Royal Adelaide Hospital.

Dr. N. J. Caldwell has been appointed an assistant medical officer of health in the Department of Health of New South Wales.

Deaths.

THE following death has been announced:

GIRI.—Devarayadoorg Venkata Giri, on November 28, 1954, at Horsham, Victoria.

Diary for the Month.

DEC. 21.—New South Wales Branch, B.M.A.: Ethics Committee.
JAN. 4.—New South Wales Branch, B.M.A.: Council Quarterly.
JAN 11.—New South Wales Branch, B.M.A.: Executive and Finance Committee.

Medical Appointments: Important Notice.

MEDICAL PRACTITIONERS are requested not to apply for any appointment mentioned below without having first communicated with the Honorary Secretary of the Branch concerned, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

New South Wales Branch (Medical Secretary, 135 Macquarie Street, Sydney): All contract practice appointments in New South Wales.

Queensland Branch (Honorary Secretary, B.M.A. House, 225 Wickham Terrace, Brisbane, B17): Bundaberg Medical Institute. Members accepting LODGE appointments and those desiring to accept appointments to any COUNTRY HOSPITAL or position outside Australia are advised, in their own interests, to submit a copy of their Agreement to the Council before signing.

South Australian Branch (Honorary Secretary, 80 Brougham Place, North Adelaide): All contract practice appointments in South Australia.

Western Australian Branch (Honorary Secretary, 205 Saint George's Terrace, Perth): Norseman Hospital; all contract practice appointments in Western Australia. All government appointments with the exception of those of the Department of Public Health.

Tasmania: Part-time specialist appointments for the north-west coast of Tasmania.

Editorial Notices.

MANUSCRIPTS forwarded to the office of this journal cannot under any circumstances be returned. Original articles forwarded for publication are understood to be offered to THE MEDICAL JOURNAL OF AUSTRALIA alone, unless the contrary be stated.

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